Mechanisms and Prevention of Pneumonia in the Elderly

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Sekizawa, K. Mechanisms and Prevention of Pneumonia in the Elderly. Tohoku J. Exp. Med., 1998, 184 (2), 73–84 —— Pneumonia is not only a major cause of death for elderly persons, but also imposes substantial personal morbidity and burdens on the health care system. An understanding of the pathogenesis of this serious illness could allow us to devise methods for curbing the incidence and severity of the disease. Pathophysiological issues and preventative measures are the subject of this review ——— oropharyngeal secretion; gastric content; silent aspiration; protective reflexes; substance P © 1998 Tohoku University Medical Press

Pneumonia is a common source of morbidity and mortality among older people despite the availability of potent new antimicrobials. In Japan, pneumonia is the fourth leading cause of death, and people over 65 years of age account for 92% of pneumonia fatality. Both the increased incidence of pneumonia and the high mortality are a consequence of a number of age-related factors including coexisting illnesses, therapeutic interventions, and the aging process itself (Ely and Haponik 1991). Since antimicrobial therapy has a limited benefit in reducing the morbidity and mortality (Ely and Haponik 1991), establishment of prevention strategies based on mechanisms of this devastating illness is essential. The purpose of this review is therefore to discuss how pneumonia develops in the elderly and to suggest preventive strategies that are promising future approaches.

Pathogenesis and predispositions

Risk factors for the development of pneumonia in the elderly can be broadly classified into the following: (1) factors that alter host defenses, and (2) factors that increase exposure to bacteria. Mortality correlates with decreased IgG levels, cutaneous anergy, and lymphopenia (Plewa 1990). Major compromises of mechanical airway clearance (e.g., impaired cough and swallowing reflexes) probably present the most severe general hazards.

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**Bacterial adherence and colonization**

Pneumonia in the elderly is thought to begin with oropharyngeal colonization that leads to aspiration and subsequently to lung infection (Bartlett 1990). Bacterial adherence to pharyngeal epithelial cells is thought to play an important role in these events. Factors such as pH, buccal versus tracheal cell type, coexisting viral infection, and type of bacteria influence this host-organ interaction (Fainstein et al. 1980; Palmer et al. 1986; Todd et al. 1989). Bacterial colonization rates among independently living community residents and those in the acute hospital ward differ considerably (9% and 60%, respectively) (Valenti et al. 1978). Factors associated with airway colonization and pneumonia include mechanical devices, cigarette smoking, underlying respiratory disease, bedridden status, and viral infection. Johanson et al. (1972) associated coma, systemic hypotension, pulmonary disease, endotracheal intubation, acidosis, azotemia, leukocytosis, and leukopenia with gram-negative colonization. Although the lower respiratory tract was once thought to be sterile, postmortem studies show oropharyngeal bacteria in up to 89% of patients (Mays et al. 1969; Toews et al. 1990). The lower respiratory tract is more frequently colonized in patients with chronic bronchitis (Valenti et al. 1978), tracheostomy, or history of heavy smoking (Palmer 1987), all common factors among the elderly.

Normal oropharyngeal flora include *Streptococcus viridans* (*Streptococcus salivarius* and *Streptococcus sanguis*), aerobic gram-negative cocci such as *Branhamella catarrhalis*, and nontypeable *Haemophilus influenzae* (Toews et al. 1990). These organisms are replaced in many recently intubated patients within 24 to 48 hours and in the majority within 1 week (Schwartz et al. 1984). Patterns of colonization frequently encountered include *Pseudomonas* in patients with tracheostomy, gram-negative bacilli in patients who are intubated, *H. influenza* and *S. pneumoniae* in patients with bronchitis, and *S. viridans* in heavy cigarette smokers. Colonization may follow the introduction of an airway device because of nonsterile technique or subsequent contamination. Colonization with the tracheotomized patient is also influenced by alterations in pH. Buccal cell adherence falls and tracheal cell adherence rises with increased pH. This suggests that bacterial adherence may be mediated by different mechanisms at each site and that buccal and tracheal sites may be colonized independently of one another (Palmer 1987).

Viral infections predispose elderly patients to subsequent bacterial infections (Schwarzmann et al. 1971). Viral-mediated changes in bacterial adherence (e.g., *S. aureus, H. influenzae, S. pneumoniae*, and *B. catarrhalis*) follow influenza A infection (Fainstein et al. 1980; Jones and Menna 1982; Sarubbi et al. 1990). Cellular desquamation, impaired ciliary function, and decreased mucociliary clearance and phagocyte function are other factors in the viral-bacterial interaction (Palmer 1987).
Aspiration

Aspiration is possibly the single most important risk factor for pneumonia in the elderly. Aspiration can be broadly defined as the misdirection of oropharyngeal contents into the larynx. However, aspiration pneumonia refers to two pathophysiologically distinct conditions that may occur more frequently in those with an impairment in oral intake, but may not be directly related to prandial aspiration. Common medical usage equates aspiration pneumonia with Mendelson's syndrome (Mendelson 1946), or the acute aspiration of gastric content (Wynne and Modell 1977). This condition occurs when depressed levels of consciousness or laryngo-pharyngeal impairment allow refluxed or vomited gastric contents to be aspirated into the lung. The respiratory and cardiovascular deterioration that results is variable, but often leads to considerable morbidity and mortality.

Aspiration pneumonia is also used to describe the bacterial infection of the lung that results from aspiration of bacteria contained in oropharyngeal (Bartlett et al. 1974; Johanson and Harris 1980) or gastric secretions (Berk et al. 1983). Such “silent aspiration” frequently occurs and is a more important cause of pneumonia than the acute aspiration of gastric content in the elderly (Feinberg et al. 1990). Usually, silent aspiration into the lungs is well tolerated. 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. The elderly patients with a predisposition to aspiration frequently aspirate oropharyngeal or gastric secretions and the development of pneumonia occurs when normal pulmonary defense mechanisms are overwhelmed (Nakagawa et al. 1997).

In a recent evaluation of 277 patients requiring mechanical ventilation for more than 24 hours, 15.5% developed pneumonia (Kollef 1993). The occurrence of pneumonia was more likely if patients had supine head position at any time during the first 24 hours of admission. Other risk factors for development of pneumonia include age older than 60 years and prior administration of antibiotics. Thus the supine position, possibly by increasing the likelihood of aspiration of gastric contents into the lung, may lead to pneumonia. Nasogastric tubes can also promote aspiration of gastric contents by impairing swallowing, causing stagnation of oropharyngeal secretions, and reducing the lower esophageal sphincter tone. Prior use of antibiotics promotes colonization of the oropharynx and gastrointestinal tract by potentially pathogenic bacteria, which can be aspirated and cause pneumonia. The normal anaerobic gastrointestinal flora creates resistance to colonization by more virulent organisms, and this “colonization resistance” is lost when antibiotics are given (Barza et al. 1987). The gastrointestinal tract has been identified as a potential source of gram-negative organisms that
reach the lung, and elevation of gastric pH (by nasogastric feeding, antacids, or H2 antagonists) is a risk factor for bacterial overgrowth in the stomach (Atherton and White 1978; Du Moulin et al. 1982; Pingleton et al. 1986). These events all lead the elderly to frequent aspiration of virulent organisms in the gastrointestinal tract, thereby causing pneumonia.

**Impaired protective reflexes and silent aspiration**

The progressive loss of protective reflexes (e.g., swallowing and cough reflexes) with age is thought to be one of the reasons 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; Pinto et al. 1994). However, re-evaluation of age-related changes in protective reflexes in individuals who led active daily lives shows that both reflexes do not decrease with the advance of age (Katsumata et al. 1995; Kobayashi et al. 1997), indicating that involutional and degenerative changes of aging often result in marginally compensated protective reflexes (Sheth and Diner 1988).

When common neuromuscular diseases affect the elderly, swallowing difficulty may present and progress differently from younger individuals. Dysphagia secondary to acute stroke is less common than progressive dysfunction due to multiple prior strokes (Feinberg et al. 1990). Multiple strokes cause dementia and aspiration is more commonly associated with dementia than specific neuromuscular disorders (Feinberg et al. 1990). Gastroesophageal reflux probably occurs more often because of the patient’s bedridden state and vomiting may be more frequent, adding to the risk of aspiration pneumonia. Elderly patients frequently have deglutition problems and aspirate during the postoperative period or when removed from ventilators. Hypoxia and small strokes are potential causes for these events (Feinberg et al. 1990).

Huxley et al. (1978) observed that 45% of normal subjects and 70% of patients with altered sensorium aspirated pharyngeal secretions during sleep. However, each subject repeatedly received bolus injections of 111indium chloride solution ten times into the pharynx via nasal catheter. The existence of the nasal catheter could disturb sleep and bolus injections of the radioactive tracer might overestimate pharyngeal aspiration in their study. A new technique using 111indium chloride to detect silent aspiration during sleep in a natural condition was developed (Kikuchi et al. 1994). By using the new technique, the role of silent aspiration in development of pneumonia in the elderly was examined in 276 patients 65 years of age or older who were admitted to a long-term care facility for 2 years (Nakagawa et al. 1997). The risk of pneumonia was significantly higher in patients with basal ganglia infarcts (e.g., twice as high after unilateral basal ganglia infarcts and 3 times as high after bilateral basal ganglia infarcts than in patients with or without cerebral hemispheric infarcts in other locations). In this
study, patients with basal ganglia infarcts showed an attenuated swallowing reflex at night and a higher incidence of silent aspiration during sleep than those without infarcts (67% in unilateral basal ganglia infarcts, 93% in bilateral basal ganglia infarcts and 13% in no infarct, respectively), suggesting that basal ganglia infarcts may predispose elderly patients to frequent aspiration due to impairments in the swallowing reflex during sleep. Furthermore, spontaneous cough has been shown to be suppressed during sleep in humans (Kuhn et al. 1982; Zheng et al. 1997). Thus, the development of pneumonia may occur as a consequence of impairments of protective reflexes during sleep in patients with cerebrovascular diseases.

**Mechanisms of impaired protective reflexes**

The receptive regions eliciting the pharyngeal and esophageal components of swallowing have been analyzed by touch and pressure stimulation (Pommerenke 1928; Storey 1968; Sinclair 1970) and liquid stimulation (Miller and Sherrington 1916; Storey 1968). The receptor regions include the soft palate, uvula, dorsal surface of the tongue, pharyngeal surface of the epiglottis, faucial pillars, glossoepiglottidinal sinus, dorsal pharyngeal wall, and the pharyngoepithelial junction. Of these, the most effective receptor regions for the elicitation of the pharyngeal phase of deglutition are innervated by fibers of the glossopharyngeal nerve, carried through the pharyngeal plexus, and by the superior laryngeal branch of the vagus (Miller 1982). Likewise, the origin of cough is unique to structures innervated by the vagus nerves. The three most likely candidates for cough receptors are the rapidly adapting pulmonary stretch receptors with small diameter myelinated fibers, and the pulmonary and bronchial C-fiber receptors with nonmyelinated afferents (Widdicombe 1995). The evidence that the rapidly adapting pulmonary stretch receptors cause cough is based on their localization at the sites of the airway most sensitive for cough (larynx and carina) (Widdicombe 1954; Das et al. 1978), the fact that all the mechanical and chemical stimuli that lead to cough also excite them (Coleridge and Coleridge 1986), and the observation that many of the nonmyelinated fibers in the epithelium are connected to myelinated fibers in the vagal trunks (Gayler 1934). However, there has been considerable discussion as to whether C-fiber receptors also cause cough (Widdicombe 1995).

The pharyngeal, laryngeal and tracheal epithelium, the sites most important for initiation of swallowing and cough reflexes, have an extensive plexus of nerves which stain substance P (Pernow 1983; Baluk et al. 1992). Capsaicin desensitization that abolishes substance P from the airway and upper digestive tract or a NK1 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 (Jin et al. 1994) in guinea pigs, suggesting an important role of substance P-containing nerves in the initiation of 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 vagus nerves (Sekizawa et al. 1996).

It is well known that dopamine agonist treatments in the rat brain bring about a heightened striosomal expression of substance P, and both dopamine D1 and D2 antagonists decrease it (Graybiel 1990). Mice lacking the dopamine D1 receptor (Xu et al. 1994) or dopamine synthesis (Zhou and Palmiter 1995) exhibited abnormal motor activities, feeding problems, and reduced substance P immunoreactive nerve fibers in the striatum. Similarly to the central nervous system, cell bodies in the nodose ganglia, dorsal root ganglia, and sensory ganglia synthesizing and transporting substance P to the laryngeal and pharyngeal mucosa may receive dopamine signaling (Kummer 1994). Chronic treatment with a dopamine D1 receptor antagonist attenuates the swallowing reflex and decreases the amount of substance P in the laryngeal and pharyngeal mucosa (Jia et al. in press), suggesting that the possible role of peripheral substance P regulated by dopamine-containing neurons to induce reflex swallowing.

In patients suffering from aspiration pneumonia with impaired protective reflexes, injections of low concentrations of capsaicin solution into the pharyngeal region, inducing substance P release from sensory nerves, stimulated swallowing reflex (Ebihara et al. 1993) and the reduction of substance P concentration in sputum was observed in such patients (Nakagawa et al. 1995). Likewise, swallowing disorder is a well-recognized feature of Parkinson’s disease (Edwards et al. 1992). Selective depletion of dopamine occurs in the neostriatum in Parkinson’s disease, and an impaired dopamine metabolism is observed in patients with infarctions in the basal ganglia (Wallin et al. 1989; Itoh et al. 1994). These patients frequently have swallowing disorders, which cause substantial morbidity and mortality due to aspiration pneumonia (Yahr 1989; Nakagawa et al. 1997). Singaram et al. (1995) demonstrated a dopaminergic defect of the peripheral nervous system in Parkinson’s disease patients with gastrointestinal dysfunction. Thus, these observations suggest a significant role of central and peripheral nervous systems containing substance P and dopamine in regulating protective reflexes in humans and a defect of these nervous systems may lead older people to aspiration pneumonia.

*Altered host defenses in the elderly*

The patient’s ability to kill and clear bacteria may be compromised, but most defenses are relatively intact (Bartlett 1990). Some of the host defects suggested in the elderly are as follows: decreases in IgM level, immunoglobulin avidity, interferon, thymic hormone levels, neutrophil chemotaxis, oxygen radical production, delayed-type hypersensitivity reaction, T-cell mitogen-induced proliferation and Langerhans’ cell number and function (Plewa 1990). However, the relation
of altered host defenses to development of pneumonia in the elderly is poorly understood. Extensive research is therefore needed for this issue.

**Antimicrobial therapy**

When older patients appear to have pneumonia, their living environments and underlying risk factors can assist in diagnosing community-acquired and nosocomial pneumonia. Since progressively higher degrees of institutionalization associated with reduced capacity for self-care and reduced physiologic reserve is a characteristic feature, older people have a high risk of nosocomial pneumonia. *S. aureus* and gram-negative bacilli are the two most important causes of nosocomial pneumonia. Although therapy is often begun without firm knowledge of the specific etiologic agent, timely and potentially life-saving therapy requires an empiric and broad spectrum approach. Even though our current knowledge of nosocomial pneumonia is incomplete, empiric therapy of nosocomial pneumonia has been endorsed by an ad hoc international consensus panel (Bassin and Niederman 1995).

**Prevention of pneumonia in the elderly**

Pneumonia in the elderly patients is associated with high morbidity and mortality. Potentially modifiable risk factors should be vigorously sought. Vaccinations, improved infection control practices and the reduction of aspiration are three of the most important prophylactic measures.

**Vaccinations.** Vaccinations to prevent pneumococcal pneumonia and influenza can have a remarkable effect on pneumonia in the elderly. Some investigations estimate a 60% to 95% prevention rate for Pneumovax (pneumococcal vaccine, polyvalent) in immunocompetent elderly and other high-risk patients (Sims et al. 1988; Wright et al. 1990). Influenza vaccine also prevents a 75% of illness in high-risk, institutionalized older persons (Wright et al. 1990). It is currently recommended that all adults 65 years or older and those at risk because of underlying illnesses receive both of these vaccines in the United States (Immunization Practices Advisory Committee 1989; Wright et al. 1990). Because of the importance of gram-negative bacilli in aspiration pneumonia, vaccines directed toward gram-negative rods such as *Pseudomonas and Klebsiella* are also needed.

**Infection control.** Improved hand-washing practices and appropriate handling of mechanical feeding, suction, and respiratory devices should reduce the spread of infectious agents in institutions. Oral hygiene practices are also important since they reduce respiratory infections in elderly bedridden patients probably due to decreases in oropharyngeal colonization (Yoneyama et al. 1996).

**Aspiration prevention.** Efforts to minimize aspiration in older patients are
imperative, although identification of the best approach is controversial. Cautious use of sedative hypnotics and avoidance of unnecessary mechanical devices for both respiratory and nutritional support should be beneficial, but from a practical standpoint, these are difficult to achieve. The avoidance of unnecessary use of antibiotics can reduce oropharyngeal colonization (Ely and Haponik 1991) and may be beneficial in the prevention of aspiration pneumonia.

A pharmacological approach to improve protective reflexes is difficult and has not been done so far. However, preliminary studies showed that injections of low concentrations of capsaicin solution into the pharyngeal region (Ebihara et al. 1993) and oral administration of an angiotensin- converting enzyme inhibitor imidapril (5 mg) for 2 weeks (Nakayama et al. in press) improved the swallowing reflex in patients with aspiration pneumonia. The capsaicin solution releases substance P from sensory nerves (Pernow 1983) and angiotensin-converting enzyme inhibitors inhibit degradation of substance P, thereby increasing the substance P concentration in the tissue (Cascieri et al. 1984). Therefore, substance P may be the mechanism involved in an improvement of the swallowing reflex in these patients. Finally, the intravenous administration of levodopa significantly improved the swallowing reflex in patients with aspiration pneumonia (Kobayashi et al. 1996). These observations have a potential relevance to pharmacological therapy for aspiration pneumonia in the elderly.

Conclusion

Pneumonia, a life-threatening disease in the elderly, continues to be a serious problem, even during the modern antibiotic era. Whenever possible, it is essential to understand the pathogenesis and establish preventative measures of pneumonia in the elderly.

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