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Diagnostic Tools and Disease Managements

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Kosaku Komiya *Editors*

Aspiration Pneumonia

The Current Clinical Giant for Respiratory Physicians

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Preface

Pneumonia is the world's leading cause of death among adults aged 65 years and older. Older people have a higher risk of getting pneumonia and are more likely to die from it if they do. For US seniors, hospitalization for pneumonia has a greater risk of death compared to any of the other top 10 reasons for hospitalization. Importantly, most of the cases should be diagnosed as nursing- and healthcare-associated pneumonia (NHCAP) rather than conventional community-acquired pneumonia (CAP). NHCAP is a new entity of pneumonia which was redefined according to ATS/IDSA guidelines. NHCAP was pathophysiologically diagnosed as aspiration pneumonia.

In many developed countries, most of the hospitalized cases of pneumonia should be diagnosed as aspiration pneumonia. Because pneumonia is the leading cause of death in the countries, all the clinicians, whether they are physicians or surgeons, face the therapeutic challenges of aspiration pneumonia. However, aspiration pneumonia is not clearly defined in pneumonia guidelines of Western countries. The therapeutic strategy is not introduced. In Japan, there is evidence of therapeutic and preventive approaches for aspiration pneumonia in the elderly. Further, the definition and its management are clearly written in healthcare-associated pneumonia guidelines by the Japanese Respiratory Society. Thus, these recent advancements in aspiration pneumonia may offer good practices in clinical settings both in Japan and in many developed countries. All the primary physicians and pulmonologists should pay attention to this disorder, because the patients with aspiration pneumonia are often in a post-stroke state and elderly. Further, many neurologists, geriatric physicians, respiratory nurses, physical therapists, dentists, and otolaryngologists are very much interested in this disease. Gerontologists and geriatricians are also concerned about these diseases. Further, many surgeons also have concerns about the type of pneumonia in association with postoperative complications and cancer therapy-related complications.

The book was meant to introduce a recent advancement of knowledge of aspiration pneumonia to all the physicians in the world.

Sir William Osler said 100 years ago that pneumonia is a friend of the aged. Elderly people are considerably more likely to suffer from pneumonia, in particular aspiration pneumonia, and often die.

This book should be useful for any practitioner who wants to treat aspiration pneumonia as well as for many patients with aspiration pneumonia who want to prevent next pneumonia events.

Tokyo, Japan — Shinji Teramoto
Oita, Japan — Kosaku Komiya
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Part I
Definition, Diagnosis and Theory of Aspiration Pneumonia

Chapter 1
Epidemiology of Aspiration Pneumonia: How Frequently Does Aspiration Pneumonia Occur in Older Adults?

Tomomi Mitsuhata and Shinji Teramoto

Abstract Aspiration pneumonia (AP) is a distinct subtype of pneumonia that significantly contributes to pneumonia-associated deaths. However, its incidence has yet to be fully elucidated. AP can occur in elderly patients with concomitant diseases and in post-surgical patients. The proportion of AP cases in community-acquired pneumonia (CAP) patients reported in previous studies was 5%–60%. The incidence of AP cases among patients with CAP was 5%–16.5% in Spain, France, and North America. On the other hand, it was 60% in Japan based on a multicenter study in 2008. These discrepancies in the findings among studies may arise from differences in the case definitions of AP and the quality of dysphagia assessment. In patients with nursing and healthcare-associated pneumonia, the AP proportion was consistently reported to be 57.8% and 63.5% in Japan.

Many patients with neurological diseases such as stroke, Parkinson's disease, and amyotrophic lateral sclerosis are also at a risk of AP. However, the incidence of AP was variable ranging from 2.4% to 44%. Dysphagia considerably affects patient prognosis.

Postoperative AP becomes a critical issue in the management of many surgeries. AP could be found in patients with head and neck cancer, esophageal cancer, cardiovascular diseases, and orthopedic surgeries. The incidence was reported to range from 1.42% to 26.2% in different surgeries.

To determine the proportion of AP in various diseases, the appropriate assessment of swallowing function in patients with pneumonia is urgently necessary for distinct diagnosis of AP in clinical settings.

Keywords Aspiration pneumonia · Community-acquired pneumonia (CAP) · Nursing and healthcare-associated pneumonia (NHCAP) · Post-stroke pneumonia · Post-surgical patients

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1 Introduction

Aspiration pneumonia (AP), which develops after the aspiration of oropharyngeal contents, differs from aspiration pneumonitis, wherein inhalation of gastric contents causes inflammation without the subsequent development of bacterial infection [1, 2]. Most cases of AP were seen in older patients with concomitant diseases and adult patients following neck and other surgeries [3–5]. Post-stroke patients and patients with various neurological diseases are also at risk of AP [6, 7]. However, the incidence of AP in these patients has not been fully elucidated. In this chapter, we comprehensively summarized the data of AP and possible AP from published articles.

2 Epidemiology of AP in Community-Acquired Pneumonia (CAP) and Nursing and Healthcare-Associated Pneumonia (NHCAP)

Pneumonia is a common clinical syndrome with well-described epidemiology and microbiology. Although AP is a distinct subtype of pneumonia, the incidence and epidemiology of AP have not been fully determined. A typical AP is a major syndrome of pneumonia in the elderly. Since the definition of AP and the performance of dysphagia assessment vary in different countries, the reports of incidence of AP are not consistent.

A case-control study conducted by Marrie TJ et al. showed that the incidence of AP was 18% in nursing home patients and 15% in patients with CAP [8]. Then, Marik PE summarized that 5%–15% of CAP cases could be diagnosed as AP based on three studies published before 2001 [2, 8–10]. However, the mean age of the published papers was less than 70 years. Elderly patients with AP may not be recruited in those studies. Lanspa et al. reported that between 1996 and 2006, the proportion of AP cases among patients with CAP was 16.5% in a single center study in the US [11]. They used the International Statistical Classification of Disease and Health Related Problems—version 9 (ICD-9) codes specific for AP and aspiration pneumonitis (507×) to define AP in the study. Further, they later reported that, between 2001 and 2012, 8.7% of patients with CAP exhibited AP by analyzing multicenter and multinational data [12]. Taylor JK and coworkers have reported that some 13.8% of the patients with CAP in their hospitalized UK cohort were classified as “at risk of aspiration” [13]. The pneumonia patients were conceivably considered as AP cases (Table 1.1).

However, the Japanese study group on aspiration pulmonary disease has reported that the incidence of AP in CAP and hospital-acquired pneumonia (HAP) was 60.1% (264/439 cases) and 86.7% (130/150 cases), respectively [14]. Three hundred and ninety-four patients of 589 patients hospitalized for pneumonia (66.8%) were diagnosed with AP. In the study, a swallowing function testing was performed

Table 1.1 AP incidence in CAP and NHCAP

Authors	Publication year	Study design	Pneumonia type	Patients number	Age (years)	AP incidence (%)
Marrie TJ et al.	1989	5-year prospective acute care hospital	CAP NHAP	719	63.2	15 18
Marik PE	2001	Reviews on three published studies	CAP	92 132 719	53 ± 16 58 ± 18 63.2	5–15
Lanspa MJ et al.	2013	Retrospective population study Single center	CAP	3094	AP 77 Non-AP 59	16.5 (510/3094)
Lanspa MJ et al.	2016	Retrospective multicenter CAP organization database	CAP	5185	AP 79 ± 22 Non-AP 69 ± 27	16.5
Taylor JK et al.	2013	Hospitalized UK cohort study	CAP	1348	AP 74 Non-AP 66	13.8
Teramoto S et al.	2008	Prospective multicenter	CAP HAP	510 150	72.6 ± 8.2	CAP 60.1 (264/439) HAP 86.7 (130/150)
Hayashi S et al.	2014	Retrospective Single center	CAP HCAP	214		46.7 (100/214)
Ishida T et al.	2011	Prospective Single center	NHCAP	173	82	57.8 (100/173)
Fukuyama H et al.	2013	Prospective Single center	NHCAP	192		63.5 (122/192)
Jeon I et al.	2019	Retrospective Single center Emergency department	CAP	1042	65.3 ± 18.8	14.2 (148/1042)

CAP community-acquired pneumonia, *NHCAP* nursing and healthcare-associated pneumonia

on 361 patients (61.2%). In addition, Hayashi et al. reported that, between 2010 and 2012, AP was diagnosed in 47.6% of patients with CAP or healthcare-associated pneumonia (HCAP) in Japan [15].

In a recent retrospective study from Korea, Joen I et al. reported that between January 1, 2016, and December 31, 2016, the proportion of AP cases among patients with CAP was 14.2% [16]. Patients with AP were identified using ICD-10 codes (J69∗). Patients with recurrent pneumonia were excluded in the study. As a result, HCAP or NHCAP cases were excluded. In addition, only 5.8% of patients with CAP in particular were examined using videofluoroscopic swallowing study (VFSS). Among the 1042 patients with CAP, 623 (59.8%) were examined by chest computed tomography (CT). They reported that 18.1% of CAP patients had AP based on chest CT results.

These discrepancies in the findings among studies may arise from differences in the case definitions of AP and performance of dysphagia assessment in pneumonia

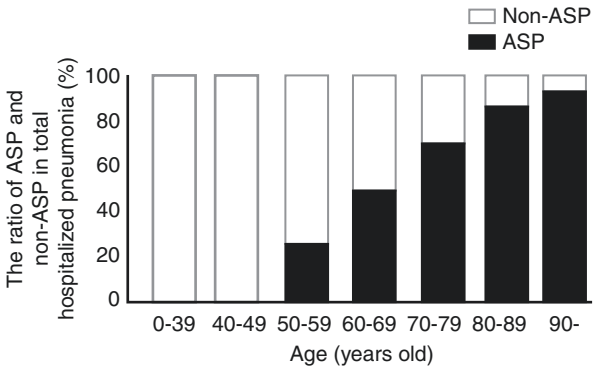

Fig. 1.1 The ratio of aspiration pneumonia (AP) and any type of pneumonia except AP (non-ASP) in total hospitalized pneumonia according to age. (Cited from Teramoto S, Fukuchi Y, Sasaki H, Sato K, Sekizawa K, Matsuse T, et al. High incidence of aspiration pneumonia in community- and hospital-acquired pneumonia in hospitalized patients: a multicenter, prospective study in Japan. J Am Geriatr Soc. 2008;56:577–9)

patients. Although the VFSS examination was found to have nearly 100% specificity and a positive predictive value for AP diagnosis, it is not commonly performed in CAP and NHCAP patients. Bedside swallowing screening tests are recommended for patients at high risk of oropharyngeal aspiration. Since most cases of AP are silent or unwitnessed, the true incidence rate is difficult to calculate.

AP is also common among residents of nursing homes. Ishida T et al. performed an etiological diagnosis in 173 patients with NHCAP in Japan. In the study, AP was diagnosed in 100 cases (57.8%) among 173 NHCAP patients [17]. A prospective study revealed that 122 cases (63.5%) were diagnosed as AP among 192 NHCAP patients in Japan [18]. AP was associated with poor outcomes and was considered a major characteristic of NHCAP.

The risk of AP increases in older adults, which is particularly relevant in the rapidly aging society of developed countries. It has been reported that the ratio of AP to total cases of pneumonia increased with age irrespective of CAP or NHCAP (Fig. 1.1).

2.1 Epidemiology of AP in Post-stroke Patients

Post-stroke infection is one of the most common complications, with 30%–65% of patients diagnosed in the postacute phase [19, 20]. AP is the most frequent source. Stroke-associated pneumonia, which is diagnosed as AP, is the leading cause of death in the 1st month after stroke, accounting for approximately 30% of the 30-day mortality. Johnson ER et al. have reported that 29 of the 60 patient study population who had qualitative and quantitative evaluations of videofluoroscopic swallowing studies developed poststroke AP [21]. Six percent of stroke patients are reported to die within the first year from AP. Ding and Logemann perfomed a retrospective study of 378 consecutive stroke patients who were referred between June 1994 and

Table 1.2 AP incidence in post-stroke patients

Authors	Publication year	Study design	Dysphagia evaluation	Patients number	Age (years)	AP incidence (%)
Johnson ER et al.	1993	Retrospective Single center Medical record review	Dynamic swallow videofluoroscopy	60	70	15 (29/60)
Ding R et al.	2001	Retrospective Single center	Videofluorographic studies	378		101/378
Dziewas R et al.	2004	Prospective Single center	Swallowing provocation test	100 With tube feeding	63.0 ± 15.8	44
Sellars C et al.	2007	Prospective Single center	Water swallow test	412	75.4 ± 11.4	18.9 (78/412)
Mao L et al.	2019	Retrospective Single center	Modified water swallow test	257	72 ± 10.8	37.7 (97/257)

June 1997 for videofluorographic study of oropharyngeal swallow. Pneumonia occurred in 101 of the stroke patients [22] (Table 1.2).

Sellars and coworkers studied 412 patients, 391 (94.9%) with ischemic stroke and 21 (5.1%) with hemorrhagic stroke; 78 (18.9%) met the study criteria for pneumonia. Patients were followed up at 3 months after stroke [23]. In an Indian study, Mao L et al. retrospectively reviewed 257 patients with acute cerebral infarction between January 2014 and December 2016. They found that 97 (37.7%) cases had post-stroke pneumonia [24].

Dziewas R et al. performed a prospective study on 100 consecutive patients with acute stroke who were given tube feeding because of dysphagia over an 18-month period [25]. Pneumonia was diagnosed in 44% of the tube-fed patients. Nasogastric tubes offer only limited protection against AP in patients with dysphagia from acute stroke. Tube feeding including percutaneous endoscopic gastrostomy (PEG) may be a risk factor for AP in post-stroke patients [26].

Oropharyngeal dysphagia (OD) is both underestimated and underdiagnosed as a cause of malnutrition and respiratory complications following stroke. OD occurs in more than 50% stroke patients. AP occurs in up to 20% of acute stroke patients and is a major cause of mortality after discharge.

2.2 Epidemiology of AP in Patients with Neurological Diseases Except Stroke

Many patients with neurological diseases except stroke are also at risk of AP. The reported prevalence of dysphagia in patients with Parkinson's disease (PD) ranges from 18.5% to 100% due to variations in methods for assessing swallowing function [27]. AP is an important cause of morbidity and mortality in PD. Martinez-Ramirez D et al.

performed a retrospective single center chart review study of 212 PD patients who had 339 hospital encounters from January 2011 to March 2013 [28]. In the 212 patients, 52 hospital encounters (15.3%) were related to a pulmonary cause. In-hospital AP events were reported in 8 (2.4%) of the total encounters. In patients with progressive supranuclear palsy (PSP), the most common cause of death is pneumonia that occurs subsequent to silent aspiration [29]. Tomita et al. reported that 90 patients with a clinical diagnosis of PSP were observed for 5.1 ± 3.8 years (mean ± SD), and 22 had AP. Subsequently, 20 patients (91%) had to discontinue oral feeding entirely and 13 (59%) died, whereas of 68 patients without pneumonia, only three patients (4%) died [30].

Patients with neuromuscular disorders are also liable to suffer from AP. Chen IJ et al. examined the medical records of 192 polymyositis (PM)/dermatomyositis (DM) patients followed up in a tertiary teaching medical center from 1999 to 2008 [31]. Seventy-six episodes of major infection, defined as infections requiring >1 week of treatment with anti-microbial agents, occurred in 53 (27.6%) patients. The incidence rate of major infections was 11.1 episodes per 100 patient-years in PM/DM patients. AP [*n* (%) = 16 (21.1)] was the leading cause of major infections (Table 1.3).

Table 1.3 AP incidence in patients with neurological and neuromuscular diseases except stroke

Authors	Publication year	Disease	Study design	Patients number	Age (years)	AP incidence (%)
Howard RS et al.	1992	Multiple sclerosis (MS)	Case series with respiratory complications	19		5.3 1/19
Chen IJ et al.	2010	Polymyositis (PM), dermatomyositis (DM)	Prospective Single center	196	63.0 ± 15.8	10.2 21/196
Martinez-Ramirez D et al.	2015	Parkinson's disease (PD)	Cross-sectional study	212	74.1 ± 10.1	Pulmonary events 15.3 (52/212) AP 2.4 (8/212)
Tomita S et al.	2015	Progressive supranuclear palsy (PSP) Retrospective Single center	Retrospective Single center	90	68.6 ± 7.1	24.4 (22/90)
Burkhardt C et al.	2017	ALS with respiratory failure	Retrospective Post-mortem study	74	62.6 ± 13.1	41.9 (31/74)

ALS amyotrophic lateral sclerosis

Patients with ALS are at a risk for AP. In epidemiological studies, respiratory dysfunction has been accountable for death in ALS up to 80%. The proportion of pneumonia in these studies has been estimated to be around 15% [32]. Burkhardt C and coworkers have examined 80 deceased ALS patients between 2003 and 2015 [33]. Respiratory failure was the main cause of death in 72 out of 74 patients. Fifteen of 74 died of AP, 23/74 of bronchopneumonia, and 8/74 of a combination of AP and bronchopneumonia.

Respiratory complications occur in advanced multiple sclerosis (MS). Howoerd RS et al. reported that one of 10 patients developed AP caused by bulbar weakness due to MS [34].

2.3 Epidemiology of AP in Post-surgical Patients

Pneumonia can be a complication of esophageal cancer. Shin J et al. analyzed 3412 esophagectomy cases, of which 812 were open and 2600 were thoracoscopic surgery [35]. Postoperative AP was seen in 4.5% of 730 patients with open surgery and 4.9% of 1271 patients with thoracoscopic esophagectomy. The preoperative oral management by dentists reduced the risk of AP to 2.2% and 3.2% of surgery, respectively. The surgery means thoracoscopic esophagectomy.

Aspiration and AP have been reported with a high incidence in head and neck cancer populations treated with chemoradiotherapy. Mortensen HR et al. reported that 18 of 324 patients developed AP and an incidence proportion of 5.3% (95% CI 3.1–8.3%) in the first year after radiotherapy [36].

Postoperative AP becomes a critical issue in the management of cardiovascular surgery in the aging society. Miyata E et al. reported that 12 (9.8%) had AP among the 123 elderly patients (>65 years old) who survived their final extubation following cardiovascular surgery at a hospital [37]. Segers P et al. have examined the efficacy of perioperative decontamination of the nasopharynx and oropharynx with 0.12% chlorhexidine gluconate for the reduction of nosocomial infection after cardiac surgery [38]. The incidence of nosocomial infection in the chlorhexidine gluconate group and placebo group was 19.8% and 26.2%, respectively. The fact indicates that the pneumonia may be primarily caused by aspiration (Table 1.4).

AP has been recognized as one of the most common postoperative complications after hip surgery in the elderly. Higashikawa T et al. have reported 18 of 426 cases (4.23%) following hip surgery [39]. Malcolm TL et al. also reported that pneumonia, respiratory failure, pulmonary embolism, and aspiration were found in 1.42% (95% CI, 1.37%–1.47%) of 2,679,351 patients who underwent total hip arthroplasty and 1.71% (95% CI, 1.66–1.76%) of 5,527,205 patients who underwent total knee arthroplasty [40].

Table 1.4 AP incidence in patients with post-surgical patients

Authors	Publication year	Disease	Study design	Patients number	Age (years)	AP incidence (%)
Segers P et al.	2008	Elective cardiothoracic surgery	Prospective, randomized, double-blind, placebo-controlled	954	65.3 ± 10.4	Chlorhexidine group 19.8 placebo group 26.2
Mortensen HR et al.	2013	Head and neck cancer after radiotherapy	Retrospective Single center	324	64 (15–92)	5.3 (18/324)
Muiyata E et al.	2017	Cardiovascular surgery	Cross-sectional study	123	74.1 ± 10.1	9.8 (12/123)
Shin J et al.	2019	Open or thoracoscopic esophagectomy	Retrospective Japanese inpatient database	Open surgery 730 Thoracoscopic Surgery 1271	66.9 ± 8.1 84.9 ± 7.4	1.42 1.71
Malcolm TL et al.	2019	Total hip arthroplasty (THA) and total knee arthroplasty (TKA)	Prospective Single center	THA TKA		1.42 1.71
Higashikawa T et al.	2020	Femoral neck and trochanteric fractures	Retrospective cohort Study	426	84.9 ± 7.4	4.23 (18/426)
Malcolm TL et al.	2019	Total hip arthroplasty (THA) and total knee arthroplasty (TKA)	Prospective Single center	THA TKA		1.42 1.71

3 Conclusion

The risk of AP increases in older adults, which is particularly relevant in the rapidly aging society of developed countries. The proportion of AP in CAP and NHCAP will increase in the future. The appropriate assessment of swallowing function in patients with pneumonia is urgently necessary for the distinct diagnosis of AP in clinical settings.

References

1. Marik PE. Aspiration syndromes: aspiration pneumonia and pneumonitis. Hosp Pract (Minneap). 2010;38(1):35–42.
2. Marik PE. Aspiration pneumonitis and aspiration pneumonia. N Engl J Med. 2001;344(9):665–71.
3. Manabe T, Teramoto S, Tamiya N, Okochi J, Hizawa N. Risk factors for aspiration pneumonia in older adults. PLoS One. 2015;10(10):e0140060.
4. Teramoto S, Kawashima M, Komiya K, Shoji S. Health care-associated pneumonia may be primary due to aspiration pneumonia. Chest. 2009;136:1702–3.
5. Teramoto S, Yoshida K, Hizawa N. Update on the pathogenesis and management of pneumonia in the elderly-roles of aspiration pneumonia. Respir Investig. 2015;53(5):178–84.
6. Teramoto S. Novel preventive and therapeutic strategy for post-stroke pneumonia. Post-stroke pneumonia. Expert Rev Neurother. 2009;9:1187–200.
7. Perry L, Love CP. Screening for dysphagia and aspiration in acute stroke: a systematic review. Dysphagia. 2001;16:7–18.
8. Marrie TJ, Durant H, Yates L. Community-acquired pneumonia requiring hospitalization: 5-year prospective study. Rev Infect Dis. 1989;11:586–99.
9. Torres A, Serra-Batlles J, Ferrer A, et al. Severe community-acquired pneumonia: epidemiology and prognostic factors. Am Rev Respir Dis. 1991;144:312–8.
10. Moine P, Vercken JP, Chevret S, Chastang C, Gajdos P. Severe community-acquired pneumonia: etiology, epidemiology, and prognosis factors. Chest. 1994;105:1487–95.
11. Lanspa MJ, Jones BE, Brown SM, Dean NC. Mortality, morbidity, and disease severity of patients with aspiration pneumonia. J Hosp Med. 2013;8:83–90.
12. Lanspa MJ, Peyrani P, Wiemken T, Wilson EL, Ramirez JA, Dean NC. Characteristics associated with clinician diagnosis of aspiration pneumonia: a descriptive study of afflicted patients and their outcomes. J Hosp Med. 2015;10:90–6.
13. Taylor JK, Fleming GB, Singanayagam A, Hill AT, Chalmers JD. Risk factors for aspiration in community-acquired pneumonia: analysis of a hospitalized UK cohort. Am J Med. 2013;126(11):995–1001.
14. Teramoto S, Fukuchi Y, Sasaki H, Sato K, Sekizawa K, Matsuse T, et al. High incidence of aspiration pneumonia in community- and hospital-acquired pneumonia in hospitalized patients: a multicenter, prospective study in Japan. J Am Geriatr Soc. 2008;56:577–9.
15. Hayashi M, Iwasaki T, Yamazaki Y, Takayasu H, Tateno H, Tazawa S, et al. Clinical features and outcomes of aspiration pneumonia compared with non-aspiration pneumonia: a retrospective cohort study. J Infect Chemother. 2014;20:436–42.
16. Jeon I, Jung GP, Seo HG, et al. Proportion of aspiration pneumonia cases among patients with community-acquired pneumonia: a single-center study in Korea. Ann Rehabil Med. 2019;43(2):121–8.

17. Ishida T, Tachibana H, Ito A, et al. Clinical characteristics of nursing and healthcare-associated pneumonia: a Japanese variant of healthcare-associated pneumonia. Intern Med. 2012;18:2537–44.
18. Fukuyama H, Yamashiro S, Tamaki H, Kishaba T. A prospective comparison of nursing-and healthcare-associated pneumonia (NHCAP) with community-acquired pneumonia (CAP). J Infect Chemother. 2013;19(4):719–26.
19. Westendorp WF, Nederkoorn PJ, Vermeij JD, Dijkgraaf MG, van de Beek D. Post-stroke infection: a systematic review and meta-analysis. BMC Neurol. 2011;11:110.
20. Rofes L, Vilardell N, Clavé P. Post-stroke dysphagia: progress at last. Neurogastroenterol Motil. 2013;25:278–82.
21. Johnson ER, McKenzie SW, Sievers A. Aspiration pneumonia in stroke. Arch Phys Med Rehabil. 1993;74:973–6.
22. Ding R, Logemann JA. Pneumonia in stroke patients: a retrospective study. Dysphagia. 2000;15(2):51–7.
23. Sellars C, Bowie L, Bagg J, et al. Risk factors for chest infection in acute stroke: a prospective cohort study. Stroke. 2007 Aug;38(8):2284–91.
24. Mao L, Liu X, Zheng P, Wu S. Epidemiologic features, risk factors, and outcomes of respiratory infection in patients with acute stroke. Ann Indian Acad Neurol. 2019;22(4):395–400. https://doi.org/10.4103/aian.AIAN_212_18.
25. Dziewas R, Ritter M, Schilling M, et al. Pneumonia in acute stroke patients fed by nasogastric tube. J Neurol Neurosurg Psychiatry. 2004;75:852–6.
26. Teramoto S, Ishii T, Yamamoto H, et al. Nasogastric tube feeding is a cause of aspiration pneumonia in ventilated patients. Eur Respir J. 2006;27:436–7.
27. Umemoto G, Furuya H. Management of dysphagia in patients with Parkinson's disease and related disorders. Intern Med. 2020;59(1):7–14. https://doi.org/10.2169/internalmedicine.2373-18.
28. Martinez-Ramirez D, Almeida L, Giugni JC, et al. Rate of aspiration pneumonia in hospitalized Parkinson's disease patients: a cross-sectional study. BMC Neurol. 2015;15:104.
29. Nath U, Thomson R, Wood R, et al. Population based mortality and quality of death certification in progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome). J Neurol Neurosurg Psychiatry. 2005;76:498–502.
30. Tomita S, Oeda T, Umemura A, et al. Impact of aspiration pneumonia on the clinical course of progressive supranuclear palsy: a retrospective Cohort study. PLoS One. 2015;10(8):e0135823. https://doi.org/10.1371/journal.pone.0135823.
31. Chen IJ, Tsai WP, Jan Wu YJ, et al. Infections in polymyositis and dermatomyositis: analysis of 192 cases. Rheumatology. 2010;49(12):2429–37.
32. Mehal JM, Holman RC, Schonberger LB, Sejvar JJ. Amyotrophic lateral sclerosis/motor neuron disease deaths in the United States, 1999–2009. Amyotroph Lateral Scler Frontotemporal Degener. 2013;14:346–52.
33. Burkhardt C, Neuwirth C, Sommacal A, Andersen PM, Weber M. Is survival improved by the use of NIV and PEG in amyotrophic lateral sclerosis (ALS)? A post-mortem study of 80 ALS patients. PLoS One. 2017;12(5):e0177555.
34. Howard RS, Wiles CM, Hirsch NP, Loh L, Spencer GT, Newsom-Davis J. Respiratory involvement in multiple sclerosis. Brain. 1992;115(Pt 2):479–94.
35. Shin J, Kunisawa S, Fushimi K, Imanaka Y. Effects of preoperative oral management by dentists on postoperative outcomes following esophagectomy: multilevel propensity score matching and weighting analyses using the Japanese inpatient database. Medicine (Baltimore). 2019;98(17):e15376.
36. Mortensen HR, Jensen K, Grau C. Aspiration pneumonia in patients treated with radiotherapy for head and neck cancer. Acta Oncol. 2013;52(2):270–6.
37. Miyata E, Tanaka A, Emori H, et al. Incidence and risk factors for aspiration pneumonia after cardiovascular surgery in elderly patients. Gen Thorac Cardiovasc Surg. 2017;65:96–101.

38. Segers P, Speekenbrink RG, Ubbink DT, et al. Prevention of nosocomial infection in cardiac surgery by decontamination of the nasopharynx and oropharynx with chlorhexidine gluconate: a randomized controlled trial. JAMA. 2006;296(20):2460–6.
39. Higashikawa T, Shigemoto K, Goshima K, Usuda D, Okuro M, Moriyama M, Inujima H, Hangyou M, Usuda K, Morimoto S, Matsumoto T, Takashima S, Kanda T, Sawaguchi T. Risk factors for the development of aspiration pneumonia in elderly patients with femoral neck and trochanteric fractures: a retrospective study of a patient cohort. Medicine (Baltimore). 2020;99(7):e19108.
40. Malcolm TL, Knezevic NN, Zouki CC, Tharian AR. Pulmonary complications after hip and knee arthroplasty in the United States, 2004-2014. Anesth Analg. 2019;130(4):917–24. https://doi.org/10.1213/ANE.0000000000004265.

Chapter 2
Clinical Significance of Aspiration Pneumonia in All the Pneumonia Therapy: The Impact of Aspiration Pneumonia on the Therapeutic Approach for All Pneumonia

Kazuhiro Yatera and Hiroshi Mukae

Abstract Pneumonia is commonly seen in all ages, but the morbidity and mortality of pneumonia increase drastically with age. A large number of pneumonia patients are the elderly who also have a high risk of aspiration. Compared to patients with non-aspiration pneumonia, patients with aspiration pneumonia show poorer prognosis, not only in the short-term but also in the long-term. The pathophysiologies of aspiration, aspiration pneumonia, and elderly pneumonia overlap, and these are very close disease entities. In addition to proper diagnosis and treatment of pneumonia in the elderly and patients with aspiration risks and aspiration pneumonia, prophylactic approach and nutritional evaluation are also important for the management of these patients. As standard diagnostic criteria of aspiration pneumonia have not been established, diagnosis of aspiration pneumonia is usually made by compatible findings on chest radiography that shows infiltrative shadows and gravity-dependent lung segments with characteristic clinical history and risk factors for aspiration. Therapeutic approach for aspiration pneumonia is the combination of antimicrobials against causative pathogens of pneumonia, treating malnutrition and comorbid illnesses, rehabilitation and reevaluation of all medications. In addition to proper diagnosis and treatment, appropriate preventive strategies such as pneumococcal and influenza vaccinations and keeping good nutrition status are necessary for better prognosis not only in patients with aspiration pneumonia but in patients with aspiration risks.

Keywords Aspiration · Aspiration pneumonia · Risk factor · Elderly · Antibiotics

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1 Introduction

Community-acquired pneumonia (CAP) is one of the most common infectious diseases requiring hospitalization and is one of the leading causes of death in developed countries around the world, and its mortality rate drastically increases with age [1–3]. In the aging Japanese population, the morbidity and mortality of pneumonia increase with age, and most patients with pneumonia are elderlies who are also at a high risk of aspiration. A meta-analysis conducted in 2016 reported that patients with aspiration pneumonia showed poorer prognosis than those with non-aspiration pneumonia, not only short-term but also long-term prognosis [4]. In another Japanese study of community-acquired and hospital-acquired pneumonia requiring hospitalization, aspiration pneumonia was more observed with age, the ratio was about 20% in the 50s, about 60% in the 70s, and about 80% in the 80s [5]. Higher rate of hospitalization and poorer prognosis of pneumonia with age are commonly seen; therefore, better understanding of the pathophysiology of aspiration pneumonia and elderly pneumonia as mimicking and overlapping disease entity is important for proper diagnosis and treatment of bacterial pneumonia in the elderly and patients with risk factors for aspiration and aspiration pneumonia.

This section outlines the points to be noted in the pathogenesis, diagnosis, treatment, and management of patients with aspiration and aspiration pneumonia and similarly of elderly patients with pneumonia.

2 Characteristics of Elderly Patients with Pneumonia

The proportion of aspiration pneumonia among patients with bacterial pneumonia increases with age; therefore, form this viewpoint, diagnosis of pneumonia in the elderly is important. Compared to younger patients with pneumonia, it may be more difficult to detect pneumonia in older patients based on the typical symptoms, such as cough, purulent sputum, general fatigue, fever and appetite loss, and pleuritic pain on deep inspiration, which are usually seen in pneumonia patients. In elderly patients with pneumonia, these respiratory or general symptoms are sometimes lacking or hard to detect, and only nonspecific symptoms such as relatively decreased appetite, altered consciousness, and delirium are observed and are the only clue to diagnosing pneumonia [6, 7]; they can also be asymptomatic. In addition, elderly people often have various underlying diseases such as cerebral infarction, dementia, chronic heart disease, hepatic disease, renal disease, and chronic obstructive pulmonary disease (COPD), and these diseases and dysfunctions make it more difficult to identify the onset of pneumonia because these conditions and complications not only obscure the clinical signs and symptoms of pneumonia but also pose as risk factors for aspiration and may cause pneumonia [7]. Furthermore, since these nonspecific symptoms may sometimes be similar in pulmonary tuberculosis and bronchiectasis including nontuberculous mycobacteriosis, careful caution must be exercised for proper diagnosis of pneumonia in the elderly.

When pneumonia requiring hospitalization occurs in elderly patients, dehydration, malnutrition, and decreased activity of daily living (ADL), causing physical cognitive decline occur after hospital admission. In addition, physical disuse progresses that causes further decline in the easily infected state and swallowing function, resulting in negative spiral that repeats further achievement of aspiration and pneumonia risks. Therefore, in addition to treating pneumonia and comorbid diseases, keeping or recovering ADL, normalization of nutrition status and physical and mental rehabilitation should simultaneously be performed in these patients.

3 Pathogenesis and Diagnosis of Aspiration Pneumonia

3.1 Pathogenesis of Aspiration Pneumonia

Aspiration pneumonia may be defined as pneumonia that develops when patients with pathological conditions prone to swallowing dysfunction repeatedly swallow oral saliva together with oral bacteria. Microaspiration may occur in about half of the healthy individuals during sleep [8–10] and is the major pathogenetic cause of pneumonia in most cases. The spectrum and combination of the volume of aspiration and repetitive aspiration events and bacterial burden in the oropharyngeal and salivary contents with the immune status of the host are determinants for the pathogenesis of aspiration pneumonia, but the magnitude of exposure to oral bacteria and salivary and gastric secretion (from macroaspiration to microaspiration) are hard to be known. Recent understanding of the microbiome in the respiratory system partly suggests that change in lung microbiota (dysbiosis and disruption of bacterial homeostasis) that impairs host defense mechanism of the lower respiratory tract and insufficient elimination of bacteria may be risk factors for bacterial immigration. In addition, change in oral bacteria in the elderly such as an increase in Gram-negative bacteria may explain the pathogenesis of aspiration pneumonia in the elderly [11]. In a study of pneumonia patients who were more than 80 years old, higher levels of serum sodium and renal dysfunction were found compared to patients without aspiration [12].

3.2 Diagnosis of Aspiration Pneumonia

Clear standard diagnosis of aspiration pneumonia has not been established so far, and clinical diagnosis of aspiration pneumonia depend on compatible findings on chest radiography that show infiltrative shadows and gravity-dependent lung segments such as superior or basal segments of lower-lobe or posterior upper-lobe segments, characteristic clinical history, and risk factors for aspiration [11]. A chest radiograph may not always detect early stages of aspiration pneumonia, and

confirmation of pneumonia infiltration and its location on computed tomography is helpful. In relation to radiological patterns of pneumonia and aspiration, Japanese pneumonia patients with fluoroscopically documented dysphagia demonstrated that 92% of them had posterior pulmonary infiltrates, and the number of patients with bronchopneumonia were more than those with lobar pneumonia (68% vs. 15%) [13]. To distinguish bacterial pneumonia from aspiration, quantitative bronchoalveolar lavage fluid (BALF) cultures, serum procalcitonin levels, and alpha-amylase levels in airway secretions are not clinically helpful. The diagnosis of aspiration pneumonia is then usually clinical.

The evaluation of swallowing function is important for the diagnosis, treatment, and management of aspiration pneumonia, and clinical methods such as simple methods performed at the bedside to endoscopic or fluoroscopic methods are used [14]. However, many of these methods of evaluating swallowing function mainly detect aspiration associated with swallowing, and non-swallowing microaspiration during sleep cannot be evaluated. Therefore, it is important to recognize the pathological condition that is likely to cause swallowing dysfunction as risk factors for aspiration pneumonia, and when patients have these basic conditions at risk of aspiration, aspiration pneumonia should clinically be considered.

4 Risk Factors for Aspiration Pneumonia

4.1 Risk Factors for Aspiration Pneumonia-Anatomical and Functional Abnormalities

In a review by Mandell et al., impaired swallowing, impaired consciousness, increased chance of gastric contents reaching the lung and impaired cough reflex are listed as risks for aspiration [11]. In relation to swallowing ability in elderly patients, oropharyngeal dysphagia strongly increased the risk of pneumonia (odds ratio, 11.9) compared with healthy elderly controls, and nearly 92% of elderly patients with pneumonia showed oropharyngeal dysphagia, and videofluoroscopic evaluation demonstrated that only 16.7% of elderly patients with pneumonia showed safe swallowing in comparison to 80% in healthy elderly controls [15] Among “impaired swallowing,” anatomical abnormalities such as esophageal disease (tumor, stenosis); COPD; neurological diseases such as seizures, multiple sclerosis, parkinsonism, stroke, and dementia; and mechanical ventilation extubation are listed [11]. COPD patients showed significantly higher rate of abnormalities of swallowing reflex compared to non-COPD patients, and COPD patients with swallowing reflex abnormalities had significantly strong symptoms of gastroesophageal reflux disease and significantly higher frequency of exacerbations [16]. In addition, “impaired consciousness” includes drug overuse, antipsychotic and narcotic medication, alcohol

consumption, and so forth. Other risks of aspiration include neuromuscular diseases such as amyotrophic lateral sclerosis and muscular dystrophy, peripheral neuropathy such as diabetic neuropathy and Guillain-Barre syndrome, muscle disorders such as myositis, and reduced perceptual sensitivity due to sedatives and hypnotics. Causes include weakness in swallowing muscles and inability to use swallowing muscles smoothly [16–19]. Medications including narcotic agents, general anesthetic agents, certain antidepressant agents, and alcohol are risk factors for impaired consciousness. In hospitalized patients, antipsychotic medications increased the risk of aspiration pneumonia by a factor of 1.5, after adjustment for other risk factors [20].

4.2 Risk Factors for Aspiration Pneumonia-Other Underlying Diseases

Nasogastric tube and gastrostomy can also be risk factors for aspiration. In general, overt aspiration and food intake do not often cause aspiration pneumonia, and aspiration may be worsened by decreased nighttime cough reflex. In addition, attention to the development of aspiration pneumonia should be paid even during fasting and also after gastrostomy [21–23]. Patients with COPD also have swallowing reflex abnormalities compared to non-COPD patients, and swallowing reflex abnormalities are positively associated with symptomatic gastroesophageal reflux disease and frequent exacerbations in COPD patients, [24].

Patients with multiple risks of aspiration and comorbid diseases have increased rates of aspiration pneumonia. In the meta-analysis of dysphagia and aspiration pneumonia in frail elders, increased odds ratio of aspiration pneumonia was observed by a factor of 9.4 and 12.9 with dysphagia and dysphagia with cerebrovascular diseases, respectively, showing combined worsening effect of risk factors [25]. In a United Kingdom cohort study, a higher 1-year mortality (hazard ratio, 1.73) and increased risks of recurrent pneumonia (hazard ratio, 3.13) and rehospitalization (hazard ratio, 1.52) were seen in patients with CAP with aspiration risks compared to patients without aspiration risks [18]. Similar results in Japanese patients with CAP identified the important risk factors for aspiration pneumonia as dementia (odds ratio, 5.20), poor performance status (odds ratio, 3.31), and use of sleeping pills (odds ratio, 2.08) [26]. In addition, increased incidence of recurrent pneumonia and increased 30-day and 6-month mortality was observed in patients with two or more risk factors for aspiration, with parallel increase in the number of risk factors.

Poor nutritional status was reported as an independent risk factor for poor outcome in institutionalized elderly patients with severe aspiration pneumonia [27]. One-third of the elderly population showed malnutrition [28], with correlation of malnutrition with sepsis, prolonged ventilator dependence [29], and increased mortality [30] being also reported. Malnutrition is related to poor prognosis.

4.3 Risk Factors for Aspiration Pneumonia-Comprehensive Assessment

In relation to the assessment of risk factors of aspiration pneumonia, swallowing function, Eastern Cooperative Oncology Group-performance status (ECOG-PS), oral hygiene, ADL, comorbid illnesses, and nutrition status are all important (Table 2.1). The frequency of aspiration increases in bedridden patients (low ECOG-PS), and Japanese prospective single center study demonstrated that patients with poor ECOG-PS 3–4 (spending more than half of the day in bed) showed significantly higher rate of aspiration pneumonia than those with good PS 0–2 (77.1% vs. 22.0%) [31]. In another Japanese study evaluating 16S rRNA gene in BALF, Akata et al. also reported that patients with aspiration risk factors showed significantly worse ECOG-PS than those without aspiration risks [32]. Furthermore, being elderly is also a risk factor for aspiration pneumonia. Laryngeal position abnormalities associated with aging such as lowering of the larynx and decreased salivary secretion are known causes of the delay and decrease in swallowing reflexes, and disordered coordination of swallowing and breathing are seen in the elderly [33–35], explaining the reasons for the increase in aspiration and aspiration pneumonia with age. In addition to swallowing dysfunction being a risk factor for aspiration pneumonia, oral hygiene is also an important factor in aspiration pneumonia; therefore, evaluating oral hygiene is important for comprehensive assessment of patients

Table 2.1 Risks for aspiration and aspiration pneumonia

Pathophysiology	Disease
Risks for aspiration	
Impaired swallowing	Impaired consciousness
	Frail, long-term bed-ridden
	Stroke
	Neurological diseases Dementia, Parkinson's disease, cerebrovascular disease
	Iatrogenic Tracheostomy, tube feeding, head and neck surgery. Sedatives, sleeping drugs, anti-cholinergics
Gastroesophageal dysfunction	Gastroesophageal reflux
	Esophageal motility disorders/esophageal stricture
	Iatrogenic Enteral feeding, Gastrectomy
Risks for aspiration pneumonia	
Impaired swallowing	Frail, long-term bed-ridden
Impaired mucocilliary clearance	Chronic airway diseases COPD, bronchiectasis, etc
Immunosuppressive state	Frail, long-term bed-ridden
	Stroke
	Malnutrition

COPD chronic obstructive pulmonary disease

suspected of aspiration and aspiration pneumonia. As one of the comprehensive evaluation tools for oral hygiene, the revised oral assessment guide (ROAG) score is used as a useful tool for oral health assessment that includes eight items in the oral cavity (voice, swallow, lips, teeth/dentures, mucous membranes, gums, tongue, saliva) evaluated in three stages (8–24 points in total) [36, 37]. Noguchi and colleagues evaluated the relationship between oral hygiene and the ROAG score and aspiration risks for elderly pneumonia patients and found that patients with high aspiration risks had poorer oral hygiene state, and patients with higher ROAG score had high aspiration risks [38]. Thus, oral hygiene is also one of the important risk factors for aspiration pneumonia.

5 Clinical Features of Patients with Aspiration Pneumonia

In the study of hospitalized Japanese pneumonia patients, both recurrence of pneumonia and hospitalized mortality rates were higher in the aspiration pneumonia group compared to the non-aspiration pneumonia group [20]. In addition, *Klebsiella pneumoniae* and *Escherichia coli* were more frequently detected in patients with aspiration pneumonia than those with non-aspiration pneumonia, but the detection rate of *Pseudomonas aeruginosa* was not different between these two groups. Another Japanese study with 98 elderly patients in the nursing-care facility showed that impaired ADL was positively significantly associated with the detection of anaerobes in bronchial aspirates [39]. In a study of 613 elderly people in a nursing-care facility in the United States, the incidence of pneumonia was 10 times higher in elderly people (>65 years old) in the nursing-care facility than in those in the community, and Cox proportional hazards model analysis showed that hazard ratios of poor oral hygiene was 1.55 (confidence interval 1.04–2.30, $p = 0.30$) and that of dysphagia was 1.61 (CI 1.02–2.56, $p = 0.43$) as independent risk factors for developing pneumonia [39].

6 Pathogens of Aspiration Pneumonia and Antimicrobial Treatment

6.1 Pathogens of Aspiration Pneumonia

Since aspiration pneumonia mainly occurs by aspiration of oral bacteria together with saliva, the main causative bacteria are the bacteria that are permanently present in the oral cavity. Anaerobes accounted for most of the causative bacteria in aspiration pneumonia in the studies in 1970s [27, 40, 41], and therefore, treatment targeting anaerobic bacteria had been recommended for aspiration pneumonia. However, in the study of the causative agent of severe aspiration pneumonia in the elderly in the

nursing-care facility performed in the United States [39], the detection rate of anaerobes was not so high (16%). Even in a comprehensive molecular analysis of BALF using the 16S ribosomal RNA (rRNA) gene for Japanese patients with healthcare-associated pneumonia [42], the detection rate of anaerobic bacteria was about 9.8%, which was slightly lower than the 15.6% from the study of patients with CAP using the same method [43]. Akata et al. [32] reported that oral streptococci were significantly higher in patients with aspiration risks, and in contrast, anaerobes were significantly higher in patients without aspiration risks (Table 2.2).

Table 2.2 The percentages of the detected bacteria by sputum cultivation, and cultivation and the bacterial floral analysis of 16S ribosomal RNA gene in bronchoalveolar lavage fluid

	Sputum culture[a]			BALF culture[a]			BALF bacterial floral analysis[b]		
		Aspiration risks (%)			Aspiration risks (%)			Aspiration risks (%)	
Pathogens	All (%)	With risks	Without risks	All (%)	With risks	Without risks	All (%)	With risks	Without risks
Gram positives									
Oral bacteria	6.5	4.4	8.5	5.6	4.8	6.3	22.3	31.0	14.7
Streptococcus pneumoniae	13.0	11.1	14.9	13.0	8.4	17.7	12.8	11.9	13.7
Staphylococcus aureus	–	–	–	–	–	–	4.5	4.8	4.2
MSSA	4.3	2.2	6.4	4.3	6.0	2.5	–	–	–
MRSA	12.0	15.6	8.5	8.6	7.2	10.1	–	–	–
Corynebacterium spp.	0.0	0.0	0.0	0.0	0.0	1.3	3.4	6.0	1.1
Gram negatives									
Haemophilus spp.	10.9	11.1	10.6	14.2	9.6	19.0	15.6	16.7	14.7
Pseudomonas aeruginosa	9.8	6.7	12.8	11.1	9.6	12.7	5.6	2.4	8.4
Klebsiella spp.	6.5	13.3	0.0	7.4	12.0	2.2	2.2	3.6	1.1
Escherichia coli	2.2	4.4	0.0	3.1	6.3	0.0	1.1	2.4	0.0
Moraxella spp.	4.3	2.2	6.4	4.3	6.0	2.2	4.5	6.0	3.2
Others									
Mycoplasma pneumoniae	–	–	–	–	–	–	7.8	2.4	12.6
Anaerobes	0.0	0.0	0.0	4.9	6.0	3.8	12.3	6.0	17.9
Oral bacteria	35.0	22.2	27.7	11.7	13.3	10.1	–	–	–
Others	4.3	6.7	4.3	11.1	10.8	11.4	7.8	7.1	8.4

All streptococci including *Streptococcus mutans* and *S. mitis*, *S. salivarius*, and *S. anginosus* were included as "oral streptococci," except for *S. pneumoniae*

BALF bronchoalveolar lavage fluid, *MSSA* methicillin-susceptible *Staphylococcus aureus*, *MRSA* methicillin-resistant *S. aureus*

[a]The numbers of patients in whom some bacterial species were cultured

[b]The bacterial floral analysis of 16S rRNA gene detected at least one or more bacterial phylotypes in all the BALF samples

6.2 Antimicrobial Treatment

Regarding the selection of antibacterial agents for treating aspiration pneumonia, oral streptococci and anaerobes, which are oral bacteria, are recognized as the main causative bacteria, and the guidelines for CAP of American Thoracic Society/Infectious Disease Society of America [1] recommend clindamycin or β-lactam antibiotics with β-lactamase inhibitors. However, recent studies have shown that anaerobic bacteria are rare in hospitalized patients suspected of aspiration [32, 39, 42, 43] from the perspective of avoiding increased resistance and increased side effects of antibiotics. A therapeutic approach with avoiding unnecessary antimicrobial treatment is now emphasized [1].

7 Conclusion

In an aging population, accurate diagnosis of aspiration pneumonia, distinguishing it from other mimicking diseases such as CAP and hospital-acquired pneumonia, is important. There are no clear diagnostic criteria for aspiration pneumonia, and careful assessment of the risk factors of aspiration and aspiration pneumonia in addition to radiological and laboratory assessments in appropriate clinical settings should always be considered, and treatment strategy with proper selection and use of antimicrobials based on these assessments may help the favorable clinical course of the patients. In addition to proper diagnosis and treatment, appropriate and careful prevention such as pneumococcal and influenza vaccinations and keeping good nutrition status is necessary for better prognosis not only in patients with aspiration pneumonia but also in patients with aspiration risks.

References

1. Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med. 2019;200:e45–67.
2. Ochoa-Gondar O, Vila-Córcoles A, de Diego C, Arija V, Maxenchs M, Grive M, et al. The burden of community-acquired pneumonia in the elderly: the Spanish EVAN-65 study. BMC Public Health. 2008;8:222.
3. Teramoto S, Yamamoto H, Yamaguchi Y, Hanaoka Y, Ishii M, Hibi S, et al. Lower respiratory tract infection outcomes are predicted better by an age >80 years than by CURB 65. Eur Respir J. 2008;31:477–8.
4. Komiya K, Rubin BK, Kadota JI, Mukae H, Akaba T, Moro H, et al. Prognostic implications of aspiration pneumonia in patients with community acquired pneumonia: a systematic review with meta-analysis. Sci Rep. 2016;6:38097.
5. Teramoto S, Fukuchi Y, Sasaki H, Sato K, Sekizawa K, Matsuse T, et al. High incidence of aspiration pneumonia in community- and hospital-acquired pneumonia in hospitalized patients: a multicenter, prospective study in Japan. J Am Geriatr Soc. 2008;56:577–9.

6. Marrie TJ. Community-acquired pneumonia in the elderly. Chest. 2004;125:801–2.
7. Riquelme R, Torres A, El-Ebiary M, de la Bellacasa JP, Estruch R, Mensa J, et al. Community-acquired pneumonia in the elderly: a multivariate analysis of risk and prognostic factors. Am J Respir Crit Care Med. 1997;156:1908–14.
8. Ramsey D, Smithard D, Kalra K. Silent aspiration: what do we know? Dysphagia. 2005;20:218–25.
9. Huxley EJ, Viroslav J, Gray WR, Pierce AK. Pharyngeal aspiration in normal adults and patients with depressed consciousness. Am J Med. 1978;64:564–8.
10. Gleeson K, Eggli DF, Maxwell SL. Quantitative aspiration during sleep in normal subjects. Chest. 1997;111:1266–72.
11. Mandell LA, Niederman MS. Aspiration pneumonia. N Engl J Med. 2019;380:651–63.
12. Pinargote H, Ramos JM, Zurita A, Portilla J. Clinical features and outcomes of aspiration pneumonia and non-aspiration pneumonia in octogenarians and nonagenarians admitted in a general internal medicine unit. Rev Esp Quimioter. 2015;28:310–3.
13. Komiya K, Ishii H, Umeki K, Kawamura T, Okada F, Okabe E, et al. Computed tomography findings of aspiration pneumonia in 53 patients. Geriatr Gerontol Int. 2013;13:580–5.
14. Teramoto S, Yoshida K, Hizawa N. Update on the pathogenesis and management of pneumonia in the elderly-roles of aspiration pneumonia. Respir Investig. 2015;53:178–84.
15. Almirall J, Rofes L, Serra-Prat M, Icart R, Palomera E, Arreola V, Clavé P. Oropharyngeal dysphagia is a risk factor for community-acquired pneumonia in the elderly. Eur Respir J. 2013;41:923–8.
16. Terada K, Muro S, Ohara T, Kudo M, Ogawa E, Hoshino Y, et al. Abnormal swallowing reflex and COPD exacerbations. Chest. 2010;137:326–32.
17. Japanese Respiratory Society. Aspiration pneumonia. Respirology. 2009;14(Suppl 2):S59–64.
18. Taylor JK, Fleming GB, Singanayagam A, Hill AT, Chalmers JD. Risk factors for aspiration in community-acquired pneumonia: analysis of a hospitalized UK cohort. Am J Med. 2013;126:995–1001.
19. Komiya K, Ishii H, Umeki K, Mizunoe S, Okada F, Johkoh T, et al. Impact of aspiration pneumonia in patients with community-acquired pneumonia and healthcare-associated pneumonia: a multicenter retrospective cohort study. Respirology. 2013;18:514–21.
20. Herzig SJ, LaSalvia MT, Naidus E, Rothberg MB, Zhou W, Gurwitz JH, Marcantonio ER. Antipsychotics and the risk of aspiration pneumonia in individuals hospitalized for non-psychiatric conditions: a cohort study. J Am Geriatr Soc. 2017;65:2580–6.
21. Hayashi M, Iwasaki T, Yamazaki Y, Takayasu H, Tateno H, Tazawa S, et al. Clinical features and outcomes of aspiration pneumonia compared with non-aspiration pneumonia: a retrospective cohort study. J Infect Chemother. 2014;20:436–42.
22. Teramoto S, Ishii T, Yamamoto H, Yamaguchi Y, Ouchi Y. Nasogastric tube feeding is a cause of aspiration pneumonia in ventilated patients. Eur Respir J. 2006;27:436–8.
23. Dennis MS, Lewis SC, Warlow C. Effect of timing and method of enteral tube feeding for dysphagic stroke patients (FOOD): a multicenter randomized controlled trial. Lancet. 2005;365:764–72.
24. Metheny NA, Meert KL, Clouse RE. Complications related to feeding tube placement. Curr Opin Gastroenterol. 2007;23:178–82.
25. van der Maarel-Wierink CD, Vanob-bergen JN, Bronkhorst EM, Schols JM, de Baat C. Meta-analysis of dysphagia and aspiration pneumonia in frail elders. J Dent Res. 2011;90:1398–404.
26. Noguchi S, Yatera K, Kato T, Chojin Y, Fujino Y, Akata K, et al. Impact of the number of aspiration risk factors on mortality and recurrence in community-onset pneumonia. Clin Interv Aging. 2017;12:2087–94.
27. El-Solh AA, Pietrantoni C, Bhat A, Aquilina AT, Okada M, Grover V, Gifford N. Microbiology of severe aspiration pneumonia in institutionalized elderly. Am J Respir Crit Care Med. 2003;167:1650–4.
28. Chandra RK. Nutritional regulation of immunity and risk of infection in old age. Immunology. 1989;64:141–7.

29. Bassili HR, Dietel M. Effect of nutrition support on weaning patients off mechanical ventilators. J Parenter Enter Nutr. 1981;5:161–3.
30. Reinhardt GF, Myscofski RD, Wilkens D, Dobrin PB, Mangan JE, Stannard RT. Incidence and mortality of hypoalbuminemic patients in hospitalized veterans. J Parenter Enter Nutr. 1980;4:357–9.
31. Ishida T, Tachibana H, Ito A, Ikeda S, Furuta K, Nishiyama A, et al. Clinical characteristics of pneumonia in bedridden patients receiving home care: a 3-year prospective observational study. J Infect Chemother. 2015;21:587–91.
32. Akata K, Yatera K, Yamasaki K, Kawanami T, Naito K, Noguchi S, et al. The significance of oral streptococci in patients with pneumonia with risk factors for aspiration. The bacterial flora analysis of 16S ribosomal RNA gene using bronchoalveolar lavage fluid. BMC Pulm Med. 2016;16:79.
33. Sekizawa K, Ujiie Y, Itabashi S, Sasaki H. Lack of cough reflex in aspiration pneumonia. Lancet. 1990;335:1228–9.
34. Nakazawa H, Sekizawa K, Ujiie Y, Sasaki H, Takishima T. Risk of aspiration pneumonia in the elderly. Chest. 1993;103:1636–7.
35. Newnham DM, Hamilton SJ. Sensitivity of the cough reflex in young and elderly subjects. Age Ageing. 1997;26:185–8.
36. Andersson P, Hallberg IR, Renvert S. Inter-rater reliability of an oral assessment guide for elderly patients residing in a rehabilitation ward. Spec Care Dentist. 2002;22:181–6.
37. Shiraishi A, Yoshimura Y, Wakabayashi H, Tsuji Y. Poor oral status is associated with rehabilitation outcome in older people. Geriatr Gerontol Int. 2017;17:598–604.
38. Noguchi S, Yatera K, Kato T, Chojin Y, Furuta N, Akata K, et al. Using oral health assessment to predict aspiration pneumonia in older adults. Gerodontology. 2018;35:110–6.
39. Quagliarello V, Ginter S, Han L, Van Ness P, Allore H, Tinetti M. Modifiable risk factors for nursing home-acquired pneumonia. Clin Infect Dis. 2005;40:1–6.
40. Bartlett JG, Gorbach SL, Finegold SM. The bacteriology of aspiration pneumonia. Am J Med. 1974;56:202–7.
41. Cesar L, Gonzalez C, Calia FM. Bacteriologic flora of aspiration-induced pulmonary infections. Arch Intern Med. 1975;135:711–4.
42. Noguchi S, Mukae H, Kawanami T, Yamasaki K, Fukuda K, Akata K, et al. Bacteriological assessment of healthcare-associated pneumonia using a clone library analysis. PLoS One. 2015;10:e0124697.
43. Yamasaki K, Kawanami T, Yatera K, Noguchi S, Fukuda K, Akata K, et al. Significance of anaerobes and oral bacteria in community-acquired pneumonia. PLoS One. 2013;8:e63103.

Chapter 3
Diagnosis of Aspiration Pneumonia: What Is the Definition of Aspiration Pneumonia in Clinical Practices?

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Abstract Aspiration is defined as the entry of oropharyngeal or gastric contents into the larynx and the lower respiratory tract. Aspiration is often the result of impaired swallowing, which allows oropharyngeal or gastric contents to enter the lungs, especially in patients who also have an ineffective cough reflex. Aspiration may involve the airways or lung parenchyma and several pulmonary syndromes may occur after aspiration, depending on the amount and nature of the aspirated material, the frequency of aspiration, and the host's response to the aspirated material. In these, aspiration pneumonia is an infectious disease caused by the inhalation of oropharyngeal secretions colonized by pathogenic bacteria, whereas aspiration pneumonitis is a chemical injury caused by inhalation of sterile gastric contents. Although there is some overlap between these syndromes, they are distinct clinical entities. In patients with aspiration pneumonia, unlike those with aspiration pneumonitis, the episode of aspiration is generally not witnessed. Thus, the diagnosis of aspiration pneumonia depends on clinical history, risk factors, and compatible findings on chest radiography. These radiographic findings include infiltrates in gravity-dependent pulmonary segments. 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.

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1 Introduction

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 comorbidities, therapeutic interventions, decreased host defense mechanisms, and site of acquisition. In these, aspiration is possibly the most important risk factor for pneumonia in the elderly. This chapter focuses on the pathophysiology, clinical features, clinical definition, and diagnosis of aspiration pneumonia and aspiration pneumonitis.

2 Definitions of Aspiration Pneumonia and Aspiration Pneumonitis in Clinical Practice

Aspiration is defined as the inhalation of oropharyngeal or gastric contents into the larynx and the lower respiratory tract [1, 2]. Aspiration is often the result of impaired swallowing, which allows oropharyngeal or gastric contents to enter the lungs, especially in patients who also have an ineffective cough reflex [1, 2]. Aspiration may involve the airways or lung parenchyma and several pulmonary syndromes may occur after aspiration, depending on the amount and nature of the aspirated material, the frequency of aspiration, and the host's response to the aspirated material [3]. In these, 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 inhalation of sterile gastric contents [3, 4]. Although there is some overlap between these syndromes, they are distinct clinical entities (Table 3.1).

Table 3.1 Characteristic features of aspiration pneumonia and aspiration pneumonitis

Features	Aspiration pneumonia	Aspiration pneumonitis
Trigger	Silent aspiration	Witnessed aspiration
Aspirated materials	Oropharyngeal secretions with bacteria	Gastric juice
Pathology	Bacterial pneumonia	Acute lung injury
Pathogens	*Enterobacteriaceae*	Acid
	Ps. aeruginosa	Pepsin
	Sta. aureus	Particulate matter
Patient	Older subjects	Adolescent or older subjects

3 Mechanisms for Development of Aspiration Pneumonia and Aspiration Pneumonitis

3.1 Aspiration Pneumonia

Although aspiration is an essential feature of aspiration pneumonia, many episodes are unwitnessed [2, 5, 6]. Such "silent aspiration" frequently occurs and is a more important cause of pneumonia than acute aspiration of gastric content in older people [7]. Silent aspiration of oropharyngeal bacterial pathogens to the lower respiratory tract is an important risk factor for community-acquired pneumonia [8] and also nosocomial pneumonia in the elderly [9].

Although approximately half of all healthy adults aspirate oropharyngeal secretion during sleep [1, 3], they are less likely to develop pneumonia because of smaller volumes or ability to clear bacteria rapidly [10]. A micro-aspiration could be a major pathogenic mechanism of most aspiration pneumonia because an extremely small volume (0.01 mL) of saliva contains pathogenic numbers of bacteria [10]. Elderly patients with a predisposition to aspiration frequently aspirate oropharyngeal secretions and the development of pneumonia occurs when normal pulmonary defense mechanisms are overwhelmed [11]. Aspiration pneumonia is usually acute, with symptoms developing within hours to a few days after a sentinel event, although anaerobic aspiration may be subacute because of the less virulent bacteria, and clinical features are difficult to distinguish from those of other bacterial pneumonias [1]. Most patients with poor performance and poor oral hygiene have diffuse and not focal infiltrates (Fig. 3.1).

Adequate protective reflexes in the airway are important and suppression or absence of these reflexes has led to pneumonia [11]. For example, Nakajoh et al. reported that the incidence of pneumonia was higher in patients having both a latency of swallowing response longer than 5 s following stimulation with 1 mL of distilled water and a cough threshold for inhalation of citric acid aerosol higher than a concentration of 1.35 (log mg mL^{-1}) [12]. Thus, the progressive loss of protective

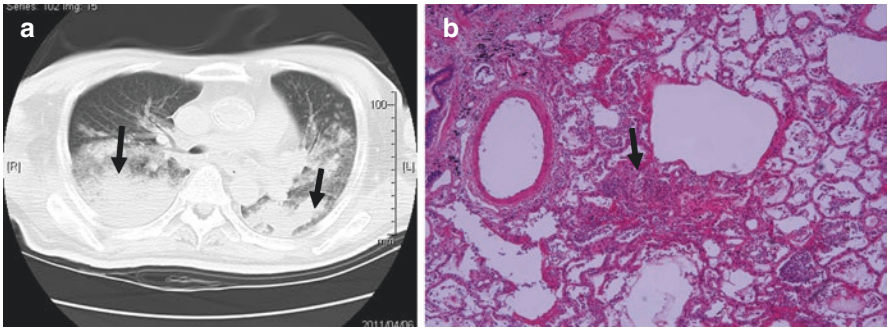

Fig. 3.1 Characteristic findings in a patient with aspiration pneumonia. The chest CT scan shows new bilateral consolidations (arrows) in posterior, gravity-dependent pulmonary segments in a patient with aspiration pneumonia (**a**). A histological examination reveals alveolar exudates and accumulation of neutrophils (arrows) along the peripheral airways (**b**)

Table 3.2 Diseases or conditions that serve as risk factors for aspiration

1.	Central nervous system diseases
	(a) Stroke
	(b) Parkinson's disease
	(c) Dementia
	(d) Epilepsy
	(e) Other neurodegenerative diseases
2.	Disturbed consciousness
3.	General anesthesia
4.	Dysphagia due to head, neck, and esophageal cancer
5.	Esophageal obstruction and motility disorders
6.	Gastroesophageal reflux
7.	Ileus
8.	COPD
9.	Overuse of anti-psychotic medications
10.	Alcohol
11.	Bedridden conditions
12.	Poor oral hygiene

reflexes (i.e. swallowing and cough reflexes) with age is thought to be one of the mechanisms for aspiration pneumonia that is often seen in older people [13]. In fact, impaired swallowing and cough reflexes have been shown in patients suffering from aspiration pneumonia [14, 15]. 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 increasing age [16, 17], indicating that involutional and degenerative changes associated with aging often result in marginally compensated protective reflexes [18].

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 [19, 20] (Table 3.2). The most important factor contributing to the development of pneumonia in patients with stroke is suggested to be dysphagia with aspiration [21]. Nakagawa et al. 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 [11]. They found that multiple episodes of pneumonia occurred frequently 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 basal ganglia infarcts [18]. 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 most important sites for the initiation of swallowing and cough reflexes, have an extensive plexus of nerves that contains substance P [22, 23]. Capsaicin desensitization, which diminishes substance P from the airway and upper digestive tract, or an administration of neurokinin (NK)-1 receptor antagonist, remarkably attenuated the cough response to tussive stimuli [24–26] and distilled water-induced swallowing reflex in guinea pigs [27],

suggesting an important role of substance P-containing nerves in the initiation of these protective reflexes [28, 29] (see Part III11). 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.

Treatment with a dopamine agonist in rats bring about a heightened striosomal expression of substance P, and both dopamine D1 and D2 antagonists decrease substance P [30]. Mice lacking the dopamine D1 receptor [31] and those treated with dopamine D1 receptor antagonist [32] showed abnormal motor activities and feeding and swallowing problems. An impaired dopamine metabolism in the basal ganglia is observed in patients with basal ganglia infarcts [33, 34]. Patients with basal ganglion infarcts or Parkinson's disease may suffer from reduced dopamine metabolism, which decreases substance P in the glossopharyngeal and vagal sensory nerves. Reduction in substance P concentration in these nerves impairs both swallowing and cough reflexes, which increases the frequency of silent aspiration. Because the action 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 [5].

3.2 Aspiration Pneumonitis

Aspiration pneumonitis occurs after a witnessed (macro)-aspiration. Aspiration pneumonitis is defined as acute lung injury after the inhalation of regurgitated sterile gastric contents [1, 3, 4]. This syndrome occurs in patients who have a marked disturbance of consciousness such as that resulting from a drug overdose, seizures, a massive cerebrovascular accident, or use of anesthesia [1, 3] (Table 3.2). Historically, the syndrome most commonly described as aspiration pneumonitis is Mendelson syndrome, reported in 1946 in patients who aspirated while receiving general anesthesia during obstetrical procedures [4].

Gastric contents can lead to chemical pneumonitis only with large-volume or low-pH (usually <2.5) aspiration [1, 3]. Later, it was shown that if the pH of gastric contents was neutralized before aspiration, the pulmonary injury was minimal [3]. It is agreed that a pH of <2.5 and a volume of gastric aspirate >0.3 mL per kilogram of body weight (20–25 mL in adults) are required for the development of aspiration pneumonitis [3]. Aspiration of particulate food matter from the stomach may cause severe pulmonary damage, even if the pH of the aspirate is >2.5 [3, 35].

Aspiration pneumonitis is characterized by a sudden onset of dyspnea, hypoxemia, tachycardia, and diffuse wheezes or crackles on examination. A chest radiograph is usually abnormal, and a pattern that is characteristic of acute respiratory distress syndrome develops in up to 16.5% of patients with witnessed aspiration [1]. Low-pH aspirates are usually sterile and bacterial infection is unusual initially, although superinfection may develop subsequently [1].

4 Risk Factors for Aspiration

Large-volume aspiration occurs with dysphagia such as head, neck, and esophageal cancer; esophageal obstruction and motility disorders; COPD; and seizures [1, 3] (Table 3.2). Additional risks include degenerative neurologic diseases such as Parkinsonism or dementia and disturbed consciousness, particularly as a result of stroke, which can also impair cough reflexes. Impaired consciousness can also result from drug overdose and medications including narcotic agents, general anesthetic agents, certain antidepressant agents, and alcohol [1, 3]. Antipsychotic medications increased the risk of aspiration pneumonia by a factor of 1.5 in a study involving 146,552 hospitalized patients [1, 3]. Enteral feeding can lead to high-volume aspiration, especially when associated with gastric dysmotility, poor cough, and altered mental status (Table 3.2). Those with two or more risk factors had an increased incidence of recurrent pneumonia and increased 30-day and 6-month mortality, with rates rising in parallel with the number of risk factors [1].

5 Diagnosis of Aspiration Pneumonia and Aspiration Pneumonitis

Aspiration pneumonia is best considered not as a distinct entity but as part of a continuum that also includes community- and hospital-acquired pneumonia. It is estimated that aspiration pneumonia accounts for 5%–15% of community-acquired pneumonia cases [1]. Robust diagnostic criteria for aspiration pneumonia are lacking, and as a result, studies of this disorder include heterogeneous patient populations. In patients with aspiration pneumonia, unlike those with aspiration pneumonitis, the episode of aspiration is generally not witnessed. The diagnosis of aspiration pneumonia depends on a history, risk factors (Table 3.2), and compatible findings on chest radiography. These radiographic findings include infiltrates in gravity-dependent pulmonary segments (superior lower lobe or posterior upper lobe segments, if the patient is in a supine position during the event, or basal segments of the lower lobe, if the patient is upright during the event) [1] (Fig. 3.1). 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 [3].

6 Conclusion

Aspiration pneumonia is an infectious process caused by the inhalation of oropharyngeal secretions that are colonized by pathogenic bacteria, whereas aspiration pneumonitis is a chemical injury caused by inhalation of sterile gastric contents. In

patients with aspiration pneumonia, unlike those with aspiration pneumonitis, the episode of aspiration is generally not witnessed. Since robust diagnostic criteria for aspiration pneumonia are lacking, the diagnosis of aspiration pneumonia depends on clinical history, risk factors, and compatible findings on chest radiography. These radiographic findings include infiltrates in gravity-dependent pulmonary segments.

References

1. Mandell LA, Niederman MS. Aspiration pneumonia. N Engl J Med. 2019;380:651–63.
2. Yamaya M, Yanai M, Ohrui T, Arai H, Sasaki H. Interventions to prevent pneumonia among older adults. J Am Geriatr Soc. 2001;49:85–90.
3. Marik PE. Aspiration pneumonitis and aspiration pneumonia. N Engl J Med. 2001;344:665–71.
4. Mendelson CL. The aspiration of stomach contents into the lungs during obstetric anesthesia. Am J Obstet Gynecol. 1946;52:191–205.
5. Ohrui T, Arai H. Aspiration pneumonia. In: Sinclair AJ, Morley JE, Vellas B, editors. Principles & practice of geriatric medicine. 5th ed. Chichester: Wiley; 2012. p. 565–72.
6. Kubo H, Nakayama K, Ebihara S, Sasaki H. Medical treatments and cares for geriatric syndrome: new strategies learned from frail elderly. Tohoku J Exp Med. 2005;205:205–14.
7. Berk SL, Verghese A, Holtsclaw SA, Smith JK. Enterococcal pneumonia: occurrence in patients receiving broad-spectrum antibiotic regimens and enteral feeding. Am J Med. 1983;74:153–4.
8. Kikuchi R, Watanabe N, Konno T, Mishina N, Sekizawa K, Sasaki H. High incidence of silent aspiration in elderly patients with community-acquired pneumonia. Am J Respir Crit Care Med. 1994;150:251–3.
9. Johanson WG, Pierce AK, Sanford JP, Thomas GD, Pierce AK. Nosocomial respiratory infections with gram-negative bacilli: the significance of colonization of the respiratory tract. Ann Intern Med. 1972;77:701–6.
10. Toews GB, Hansen EJ, Strieter RM. Pulmonary host defenses and oropharyngeal pathogens. Am J Med. 1990;88:20S–4S.
11. Nakagawa T, Sekizawa K, Arai H, Kikuchi R, Manabe K, Sasaki H. High incidence of pneumonia in elderly patients with basal ganglia infarction. Arch Intern Med. 1997;157:321–4.
12. Nakajoh K, Nakagawa T, Sekizawa K, Matsui T, Arai H, Sasaki H. Relation between incidence of pneumonia and protective reflexes in post-stroke patients with oral or tube feeding. J Intern Med. 2000;247:39–42.
13. Pontoppidan H, Beecher HK. Progressive loss of protective reflexes in the airway with the advance of age. JAMA. 1960;174:2209–13.
14. Sekizawa K, Ujiie Y, Itabashi S, Sasaki H, Takishima T. Lack of cough reflex in aspiration pneumonia. Lancet. 1990;335:1228–9.
15. Nakazawa H, Sekizawa K, Ujiie Y, Sasaki H, Takishima T. Risk of aspiration pneumonia in the elderly. Chest. 1993;103:1636–7.
16. Katsumata U, Sekizawa K, Ebihara T, Sasaki H. Aging effects on cough reflex. Chest. 1995;107:290–1.
17. Kobayashi H, Sekizawa K, Sasaki H. Aging effects on swallowing reflex. Chest. 1997;111:1466.
18. Sheth N, Diner WC. Swallowing problems in the elderly. Dysphagia. 1988;2:209–15.
19. Walker AE, Robins M, Weinfeld FD. Clinical findings: the national survey of stroke. Stroke. 1981;12(Suppl.1):113–37.
20. Kobayashi S, Okada K, Koide H, Bokura H, Yamaguchi S. Subcortical silent brain infarction as a risk factor for clinical stroke. Stroke. 1997;28:1932–9.
21. Horner J, Massey EW, Riski JE, Lathrop DL, Chase KN. Aspiration following stroke: clinical correlates and outcome. Neurology. 1988;38:1359–62.
22. Pernow B, Substance P. Pharmacol Rev. 1983;35:85–141.

23. Baluk P, Nadel JA, McDonald DM. Substance P-immunoreactive sensory axons in the rat respiratory tract: a quantitative study of their distribution and role in neurogenic inflammation. J Comp Neurol. 1992;319:586–98.
24. Ujiie Y, Sekizawa K, Aikawa T, Sasaki H. Evidence for substance P as an endogenous substance causing cough in Guinea pigs. Am Rev Respir Dis. 1993;148:1628–32.
25. Sekizawa K, Ebihara T, Sasaki H. Role of substance P in cough during bronchoconstriction in awake Guinea pigs. Am J Respir Crit Care Med. 1995;151:815–21.
26. Ebihara T, Sekizawa K, Ohrui T, Nakazawa H, Sasaki H. Angiotensin-converting enzyme inhibitor and danazol increase sensitivity of cough reflex in female Guinea pigs. Am J Respir Crit Care Med. 1996;153:812–9.
27. Jin Y, Sekizawa K, Fukushima T, Morikawa M, Nakazawa H, Sasaki H. Capsaicin desensitization inhibits swallowing reflex in Guinea pigs. Am J Respir Crit Care Med. 1994;149:261–3.
28. Ohrui T. Preventive strategies for aspiration pneumonia in elderly disabled persons. Tohoku J Exp Med. 2005;207:3–12.
29. Nakagawa T, Ohrui T, Sekizawa K, Sasaki H. Sputum substance P in aspiration pneumonia. Lancet. 1995;345:1447.
30. Graybiel AM. Neurotransmitters and neuromodulators in the basal ganglia. Trends Neurosci. 1990;13:244–54.
31. Xu M, Moratalla R, Gold LH, Hiroi N, Koob GF, Graybiel AM, Tonegawa S. Dopamine D1 receptor mutant mice are deficient in striatal expression of dynorphin and in dopamine-mediated behavioral responses. Cell. 1994;79:729–42.
32. Jia YX, Sekizawa K, Ohrui T, Nakayama K, Sasaki H. Dopamine D1 receptor antagonist inhibits swallowing reflex in Guinea pigs. Am J Phys. 1998;274:R76–80.
33. Itoh M, Ido T, Sasaki H, Meguro K. First signs of Alzheimer's? Science. 1993;259:898.
34. Itoh M, Meguro K, Fujiwara T, Hatazawa J, Iwata R, Ishiwata K, Takahashi T, Ido T, Sasaki H. Assessment of dopamine metabolism in brain of patients with dementia by means of 18F-fluorodopa and PET. Ann Nucl Med. 1994;8:245–51.
35. Ohrui T, Yamaya M, Suzuki T, Sekizawa K, Funayama T, Sekine H, Sasaki H. Mechanisms of gastric juice-induced hyperpermeability of the cultured human tracheal epithelium. Chest. 1997;111:454–9.

Chapter 4
Chest Radiographic and Chest CT Images of Aspiration Pneumonia: Are the Image Features of Aspiration Pneumonia Different from Those of Non-aspiration CAP or HAP?

Kosaku Komiya and Jun-Ichi Kadota

Abstract Aspiration pneumonia typically presents as bronchopneumonia with gravity dependence, but the sensitivity and specificity of these features are unknown. Conventional chest radiography seems to be limited for detecting pneumonia in elderly patients with low levels of physical activity. Chest CT may be indicated for such patients with suspected pneumonia, but abnormal features do not always reflect acute inflammation, especially when a patient has swallowing dysfunction. Pneumonia should be diagnosed not only from radiological features but also based on clinical symptoms and signs. Chest shadowing with gravity dependence may not be specific to aspiration pneumonia, but it may be helpful for the diagnosis of aspiration pneumonia in conjunction with screening for aspiration risks.

Keywords Radiography · CT · Aspiration pneumonia · Community-acquired pneumonia · Hospital-acquired pneumonia

1 Introduction

Pneumonia is diagnosed from clinical symptoms and evidence of abnormal shadowing on radiological images. Aspiration pneumonia is considered to exhibit a gravity-dependent distribution; however, it is uncertain whether this finding is

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specific to aspiration pneumonia as opposed to non-aspiration pneumonia. CT imaging is widely acquired in current clinical practice, and its role in diagnosing pneumonia has been compared to that of chest radiography; indeed, studies have reported pneumonia identified by CT in elderly patients with negative chest radiographs. This chapter reviews the radiological features of aspiration pneumonia, the differences in performance between chest radiography and CT, and the radiological features associated with the various causative pathogens of aspiration pneumonia.

2 Definition of Aspiration Pneumonia

Pneumonia is a pulmonary infectious disease caused by bacterial or viral infection through aspiration, inhalation, or direct invasion through the thoracic wall [1], although direct invasion through the pleura is rarely observed. Virus and *Mycoplasma pneumoniae* infections can result from the inhalation of these pathogens into the lower airways, but it is thought that other bacterial pathogens first colonize the laryngopharynx, from where they are then aspirated into the lungs. Thus, most bacterial pneumonias can be considered to be aspiration pneumonia in terms of their development mechanism. However, many physicians consider aspiration pneumonia to be a type of pneumonia that develops in patients with swallowing dysfunction [2–4].

Because of the difficulties in detecting the ongoing development of pneumonia by aspiration, there is no clear definition of aspiration pneumonia, with published studies using a variety of definitions [4]. Most of the definitions used in those studies included the presence of aspiration risks and/or swallowing dysfunction confirmed by videofluoroscopic or videoendoscopic examination [5–7]. Aspiration risks include cerebrovascular disorders, dementia, recent neck surgery, gastroesophageal reflux, and low levels of physical activity; however, the severity of these conditions can vary [8]. Furthermore, swallowing function confirmed by videofluoroscopy or videoendoscopy can subsequently change according to the patient's level of consciousness or nutritional status [9]. It is important to remain aware of the uncertainty in the definition of aspiration pneumonia when considering this subject.

Aspiration pneumonia can be community-acquired or hospital-acquired, and populations with aspiration risks are at higher risk of the condition. Ventilator-associated pneumonia, which may be a type of hospital-acquired pneumonia (HAP), is characterized by aspiration pneumonia resulting from the aspiration of oral secretions [10]. These relationships are summarized in Fig. 4.1.

3 Radiological Features of Aspiration Pneumonia

Aspiration pneumonia is caused by the aspiration of oral secretions that contain bacterial pathogens. This process is gravity-dependent, so the region of the lung most likely to be affected is the lower segments [2, 11, 12]. The right main bronchus

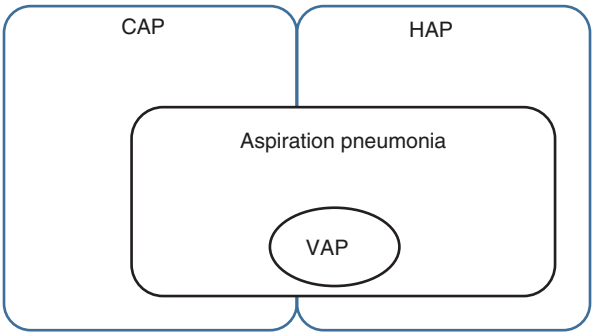

Fig. 4.1 The relationships between aspiration pneumonia and community-acquired, hospital-acquired, and ventilator-associated pneumonias

Table 4.1 Chest CT features of aspiration pneumonia

Bronchopneumonia > lobar pneumonia
Gravity-dependent distribution Lower > upper lung segments Anterior > posterior lung segments
Right > left lung segments
Pleural effusion of around 10%–60%

is wider and more vertical than the left main bronchus, so it is more susceptible to aspiration pneumonia. Aspirated bodies and aspiration pneumonia are more commonly reported in the right lung in both adults and children [13, 14]. In older people who are bedridden, the affected region may instead be the posterior upper to lower lobes [11], consistent with a gravity-dependent distribution. The typical findings of aspiration pneumonia on chest radiological images are summarized in Table 4.1.

Studies have evaluated chest CT features in patients with swallowing dysfunction but not pneumonia [15]. Compared with controls, these patients more frequently exhibited bronchiectasis, ground-glass attenuation, consolidation, atelectasis, and centrilobular small nodules [16]. This implies that if a patient with dysphagia shows abnormal features on radiological images, he or she may not always require specific treatment based on those features. Physicians need to be aware of this to reduce the unnecessary use of antibiotics and the consequent risk of antimicrobial resistance.

Microaspiration can occur during sleep, generally without any respiratory symptoms [17]. Diffuse aspiration bronchiolitis (DAB), which pathologically resembles diffuse pulmonary bronchiolitis, is a condition characterized by the chronic inflammation of bronchioles caused by the repeated aspiration of foreign particles [18]. Matsuse et al. reported that dysphagia was confirmed in only half of DAB cases, whereas two-third were bedridden with neurological disorders or dementia. Gastroesophageal reflux is a significant risk factor for DAB, even in younger adults [19]. Seven of 20 DAB patients in a recent case series experienced gastroesophageal reflux [20]. Recurrent microaspiration may occur as silent aspiration, especially during sleep. The subsequent host–pathogen interaction results in the chronic

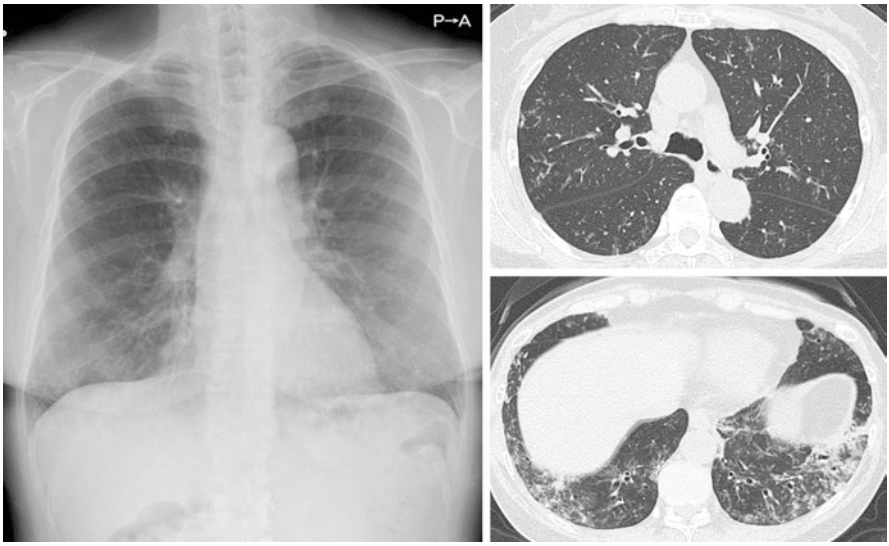

Fig. 4.2 Radiological features of diffuse aspiration bronchiolitis

inflammation of bronchioles without significant symptoms or elevated inflammation, which is associated with the development of DAB (Fig. 4.2).

A study of the "tree-in-bud" pattern on CT, which is characterized by multiple areas of centrilobular nodules with a linear branching pattern, reported that 67.5% of cases were suspected to have an infectious etiology and 10.4% were considered to be aspiration pneumonia [21]. When a patient presents with the tree-in-bud pattern, especially with gravity dependence, the physician should consider not only atypical pathogens or mycobacterium infection, but also swallowing dysfunction.

4 Chest Radiography Versus CT for the Detection of Pneumonia

The use of CT imaging is now widespread in clinical practice, and its ability to detect pneumonia has been compared with that of chest radiography [13, 22–25]. Table 4.2 summarizes several studies in which patients underwent both CT imaging and chest radiography. These mainly focused on cases of community-acquired pneumonia (CAP).

In a multicenter prospective surveillance study of 2251 adults hospitalized with CAP, Upchurch et al. compared the presenting clinical features and outcomes of patients with pneumonia observed on CT imaging but not on concurrent chest radiographs ("CT-only pneumonia") with those whose pneumonia was visualized on chest radiography [22]. Their study included 66 cases (3%) of CT-only pneumonia. These patients were significantly younger than the others and had lower levels of

Table 4.2 Summary of studies reporting patient populations that included cases of CT-only pneumonia (i.e., with negative chest radiographs)

Study	Nationality	Population	Proportion of CT-only pneumonia
Upchurch, 2018	USA	Hospitalized adults (aged ≥18 years) with community-acquired pneumonia	66/2251 (3%)
Haga, 2016	Japan	Hospitalized patients aged ≥65 years with community-acquired pneumonia	12/127 (9.4%)
Miyashita, 2015	Japan	Hospitalized nursing and healthcare-associated pneumonia	Overall: 59/208 (28%)
		Group A: Pneumonia diagnosed in residents of an extended care facility or nursing home	Group A: 27/97 (28%)
		Group B: Pneumonia diagnosed in patients discharged from a hospital within the preceding 90 days	Group B: 21/79 (27%)
		Group C: Pneumonia diagnosed in elderly or disabled people with an eastern cooperative oncology group performance status of 3 or 4, who are receiving nursing care	Group C: 50/136 (37%)
		Group D: Pneumonia diagnosed in outpatients receiving regular endovascular treatment (dialysis, antibiotic therapy, chemotherapy, and/or immunosuppressant therapy)	Group D: 1/17 (6%)
Seo, 2018	South Korea	Hospitalized immunocompetent patients with community-acquired pneumonia	94/1925 (4.9%)
Esayag, 2010	Israel	Hospitalized bedridden patients with suspected pneumonia	11/31 (35%)

procalcitonin, but there were no statistically significant differences in other clinical and pathological parameters, intensive care unit admission, the use of mechanical ventilation, septic shock, or in-hospital mortality. These findings suggested that it is likely that CT-only pneumonia reflects early-phase pneumonia in younger adults.

A retrospective study of 1925 patients with CAP in South Korea reported that 94 (4.9%) had CT-only pneumonia [25]. The radiological findings for CT-only pneumonia tended to be located in the dependent lung and these patients were characterized by a higher frequency of aspiration pneumonia than that in the remaining CAP patients, as well as a lower incidence of complication by parapneumonic effusion or empyema and pleural drainage, and lower blood levels of inflammatory markers. Despite the shorter length of hospital stay with CT-only pneumonia, 30-day and in-hospital mortality were almost the same between the two groups. The authors suggested that chest CT scans should be acquired for patients with suspected CAP but with a negative chest radiograph, especially for those who are bedridden.

A prospective study from Japan that enrolled 127 patients with CAP aged 65 years or older reported that 12 (9.4%) had CT-only pneumonia and that bilateral pneumonic infiltration on CT was a significant predictor of poor prognosis [26]. A study that investigated the detection failure rate of chest radiography for the identification of nursing home-associated pneumonia and HAP reported that 28%

(59/208) of the patients included in the study had CT-only pneumonia [13]. The subgroup of patients with the highest proportion of CT-only pneumonia cases (37%) included those who had poor performance status and who were receiving nursing home care [13] (Table 4.2). This subgroup included a large number of patients aged over 75 years with cerebrovascular disease and poor functional status. As the authors pointed out, physicians might underestimate pneumonia shadows in the chest radiographs of patients with lower physical activity levels.

Esayag et al. prospectively assessed the diagnostic value of chest radiography for the diagnosis of pneumonia in bedridden patients, using high-resolution chest CT as the gold standard, and reported a sensitivity of 65%, specificity of 93%, and positive and negative predictive values of 83% and 65%, respectively [23]. They concluded that, for bedridden patients with suspected pneumonia, a negative chest radiograph does not rule out the diagnosis of pneumonia.

In summary, these studies have shown that the detection rate for pneumonia using chest radiography is significantly lower than that using CT in the very early phase of pneumonia for younger patients and in all phases of pneumonia among older people who are bedridden. Aspiration pneumonia is a major type of pneumonia in elderly patients and is commonly distributed in a gravity-dependent manner, such as in the posterior parts of the lower segments. This can make it difficult to detect by frontal radiography due to the overlap with the diaphragm. Physicians may therefore underestimate pneumonia in chest radiographs for these patients. Conversely, lung involvement in patients with swallowing dysfunction but not pneumonia may include bronchiectasis, ground-glass opacity, and consolidation [16]. It is impossible to distinguish whether these features are acute inflammation or old inflammation with chronic changes [27]. Typical clinical symptoms and signs may be observed less frequently in older populations than in younger patients with pneumonia [28]. Physicians should not diagnose pneumonia by radiological features alone; it should be comprehensively diagnosed by taking into consideration clinical symptoms and signs, and patients should be screened for other focuses of inflammation, especially when there are no respiratory symptoms [29].

A further consideration is whether chest CT imaging should be acquired for all patients with pneumonia, even for those already diagnosed with pneumonia by chest radiography. Banker et al. assessed the impact of chest CT on the clinical management of immunocompetent patients diagnosed with pneumonia by chest radiography and found that eight of the 51 patients (16%) had alternative or additional diagnoses based on CT, including pulmonary embolism, lung cancer, hypersensitivity pneumonitis, multiple myeloma, renal cell carcinoma, small bowel obstruction, lung nodule, and endobronchial mass (one case of each) [30]. An important role of chest CT is to provide information that is useful for differential diagnoses, such as infection by atypical pathogens and other non-infectious diseases.

Empyema requires quick thoracic drainage together with the administration of appropriate antibiotics. Chest CT is not always needed for the diagnosis of empyema; ultrasound is more sensitive than chest radiography for indicating an effusion, and in some cases, it can be used to guide catheter placement for drainage treatment [31, 32].

There is no clear evidence that chest CT is beneficial for distinguishing pneumonia caused by atypical pathogens such as *M. pneumoniae*, *Legionella pneumophila* (*L. pneumophila*), and *Chlamydia pneumoniae* from pneumonia caused by general bacteria. Pulmonary tuberculosis is characterized by granulomatous inflammation of the lungs with tree-in-bud lesions, nodules, and cavitation in the upper lung segments [33]. However, elderly patients may present atypical features, and coinfection with general bacteria mimicking aspiration pneumonia is often seen, complicating the diagnosis of pneumonia but not general pneumonia in elderly patients [34–36]. Some studies have suggested that chest CT can be beneficial for identifying lung involvement in immunocompromised patients and for excluding non-infectious lung diseases such as malignancy and pulmonary alveolar proteinosis [37, 38]. However, the acquisition of chest CT for all patients with suspected pneumonia remains controversial. Chest CT to screen for pneumonia should be considered for patients with respiratory symptoms but no shadowing on chest radiography or for those with shadowing on chest radiographs but no significant respiratory symptoms and no other focus of inflammation.

5 Do the Chest Radiological Features of Aspiration Pneumonia Differ from Those of Non-aspiration CAP or HAP?

Aspiration pneumonia predominantly presents a bronchopneumonia pattern with a gravity-dependent distribution [11, 13]. However, there have been no studies that have directly compared aspiration pneumonia with non-aspiration CAP or HAP, so the sensitivity and specificity of these features for discriminating aspiration pneumonia from non-aspiration pneumonias remain uncertain. Analyses of the radiological features of pneumonia have focused on the pattern of pneumonia and the frequency of specific features such as ground-glass opacity, consolidation, or effusion, but not their distribution. Hence, there are no data about the proportions of CAP or HAP patients who exhibit the typical radiological pattern of aspiration pneumonia.

However, some studies have surveyed the rate of clinically diagnosed aspiration pneumonia among patients with CAP or HAP. Teramoto et al. prospectively assessed the prevalence of aspiration pneumonia in CAP and HAP in 589 hospitalized patients (mean ± standard deviation age, 72.6 ± 8.2 years) from 22 hospitals in different areas of Japan [39]. They reported the incidence of aspiration pneumonia in CAP and HAP to be 60.1% and 86.7%, respectively, with the incidence increasing with advancing age. A systematic review reported that 6.1%–53.2% of patients with CAP had aspiration pneumonia and that patient backgrounds and the definition of aspiration pneumonia or aspiration risk varied [4]. It is unclear whether these cases diagnosed as aspiration pneumonia exhibited the bronchopneumonia pattern with gravity dependence, but some of the included studies required gravity-dependent

shadowing on chest radiographs or CT for the diagnosis of aspiration pneumonia. Thus, these figures might closely reflect the proportion of cases that show the typical aspiration pneumonia pattern on chest images.

6 Causative Pathogens and Features of Aspiration Pneumonia on Chest CT

As has already been described, published studies regarding the imaging features of pneumonia have mainly focused on the pattern of pneumonia and the frequency of specific radiological features for each pathogen strain, but not on their distributions. The causative pathogens for aspiration pneumonia have been investigated [40–45]. The most frequently isolated aerobic Gram-positive bacteria are *Streptococcus pneumoniae* and *Staphylococcus aureus*, followed by other *Streptococcus* spp. The main aerobic Gram-negative bacteria are *Klebsiella pneumoniae* and *Escherichia coli*, followed by *Haemophilus influenzae*, *Pseudomonas aeruginosa*, and *Enterobacter* spp. Anaerobic bacteria include *Prevotella* spp., *Fusobacterium* spp., *Bacteroides* spp., and *Peptostreptococcus* spp. It has been reported that 9%–21% of isolated pathogens for aspiration pneumonia are anaerobic, but the impact of these isolates on aspiration pneumonia remains under debate [42, 44, 45].

Pneumonia caused by *S. pneumoniae* typically shows a lobar pneumonia pattern rather than bronchopneumonia, and around 10% of cases are complicated by pleural effusion [46–48]. *S. aureus* is predominantly isolated from hospitalized patients, and it can present as bronchopneumonia with the tree-in-bud pattern [49], consistent with the pattern for aspiration pneumonia. Indeed, it is well established that *S. aureus* colonizes the nose and mouth, making it a risk for aspiration [50]. *K. pneumoniae* is also commonly isolated in patients with HAP. Alcohol abuse and chronic respiratory disorders are risk factors for pneumonia caused by this strain [51, 52]; these can also be considered as risk factors for aspiration [8, 53, 54]. Pneumonia caused by *K. pneumoniae* typically exhibits the lobar pneumonia pattern in CAP and the bronchopneumonia pattern in HAP [55]. This strain is undoubtedly a major pathogen of aspiration pneumonia and so would be expected to present as bronchopneumonia with gravity dependence. Pneumonia caused by *E. coli* is often isolated from bedridden or hospitalized patients and presents with the bilateral bronchopneumonia pattern [56, 57]. This strain originates from the intestines, so it would have been aspirated through gastroesophageal reflux or by oral intake from contaminated equipment or fingers. *H. influenzae* is predominantly isolated from patients with CAP, especially in patients with chronic respiratory diseases, and it is known to be a trigger pathogen for the exacerbation of chronic obstructive pulmonary disease [58]. Patients with *H. influenzae* pneumonia present both the lobar pneumonia pattern and the bronchopneumonia pattern equivalently [59]. This strain can colonize the laryngopharynx and cause sinusitis and otitis media, from where it may descend

into and colonize the lower airways in patients with chronic respiratory diseases. *P. aeruginosa* accounts for around 20% of HAP and predominantly exhibits the bronchopneumonia pattern [32, 60]. This pathogen can colonize not only the upper airways but also the lower airways, especially in patients with bronchiectasis or cystic fibrosis [61–63]. Abscess formation with cavitation and pleural effusion is seen in around 20% of cases [64].

Anaerobic bacterial infections account for 21% of hospitalized CAP cases and 35% of HAP cases [44, 65, 66]. These infections commonly present the bronchopneumonia pattern, with abscess formation and cavitation observed in around 50% of cases, and empyema or pleural effusion in around 30% [67].

In summary, the causative pathogens of aspiration pneumonia and their radiological features vary. The etiological and radiological features of some strains are consistent with aspiration pneumonia, but there is overlap between these pathogens and those seen in commonly isolated general CAP or HAP. The bronchopneumonia pattern with gravity dependence may not always indicate aspiration pneumonia. However, pneumonia caused by *S. pneumoniae* and *L. pneumoniae* tends to present with a lobar pneumonia pattern with or without a gravity-dependent distribution rather than as bronchopneumonia, which is significantly different from the aspiration pneumonia pattern. The evaluation of radiological findings is not a perfect approach for establishing causative pathogens, but having aspiration risks can be suspected when a gravity-dependent distribution is observed.

7 Conclusions

This chapter has discussed the radiological features of aspiration pneumonia, highlighting differences with the features of non-aspiration CAP and HAP. No studies have directly compared the radiological features of aspiration pneumonia with those of non-aspiration pneumonia, so the diagnostic value of the aspiration pneumonia pattern on chest imaging is uncertain. Pneumonia in bedridden patients implies aspiration pneumonia, and this may be missed on conventional chest radiography alone. Chest CT evaluations can indicate whether these patients have suspected pneumonia, but physicians should be aware that abnormal findings in patients with swallowing dysfunction do not always reflect acute inflammation. Pneumonia should be diagnosed not only based on radiological features but also from clinical symptoms and signs. A gravity-dependent distribution on chest imaging may not be specific for aspiration pneumonia; however, when this distribution is presented, screening for aspiration risks and an evaluation of swallowing function may be beneficial for considering the pathogenesis of pneumonia.

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References

1. Fraser RS, Paré PD. Fraser and Pare's diagnosis of diseases of the chest. 4th ed. Philadelphia: WB Saunders; 1999.
2. Mandell LA, Niederman MS. Aspiration pneumonia. N Engl J Med. 2019;380(7):651–63.
3. Prather AD, Smith TR, Poletto DM, Tavora F, Chung JH, Nallamshetty L, et al. Aspiration-related lung diseases. J Thorac Imaging. 2014;29(5):304–9.
4. Komiya K, Ishii H, Kadota J. Healthcare-associated pneumonia and aspiration pneumonia. Aging Dis. 2015;6(1):27–37.
5. Fukuyama H, Yamashiro S, Tamaki H, Kishaba T. A prospective comparison of nursing- and healthcare-associated pneumonia (NHCAP) with community-acquired pneumonia (CAP). J Infect Chemother. 2013;19(4):719–26.
6. Miyashita N, Akaike H, Teranishi H, Kawai Y, Ouchi K, Kato T, et al. Evaluation of serological tests for diagnosis of Chlamydophila pneumoniae pneumonia in patients with nursing and healthcare-associated pneumonia. J Infect Chemother. 2013;19(2):249–55.
7. Ishida T, Tachibana H, Ito A, Yoshioka H, Arita M, Hashimoto T. Clinical characteristics of nursing and healthcare-associated pneumonia: a Japanese variant of healthcare-associated pneumonia. Intern Med. 2012;51(18):2537–44.
8. van der Maarel-Wierink CD, Vanobbergen JN, Bronkhorst EM, Schols JM, de Baat C. Risk factors for aspiration pneumonia in frail older people: a systematic literature review. J Am Med Dir Assoc. 2011;12(5):344–54.
9. Hirose M, Komiya K, Kadota J. Influence of appetite and continuation of meals on the prognosis of elderly patients who have lost swallowing function. J Palliat Med. 2014;17(3):259–60.
10. Karacaer F, Hamed I, Ozogul F, Glew RH, Ozcengiz D. The function of probiotics on the treatment of ventilator-associated pneumonia (VAP): facts and gaps. J Med Microbiol. 2017;66(9):1275–85.
11. Komiya K, Ishii H, Umeki K, Kawamura T, Okada F, Okabe E, et al. Computed tomography findings of aspiration pneumonia in 53 patients. Geriatr Gerontol Int. 2013;13(3):580–5.
12. Franquet T, Gimenez A, Roson N, Torrubia S, Sabate JM, Perez C. Aspiration diseases: findings, pitfalls, and differential diagnosis. Radiographics. 2000;20(3):673–85.
13. Miyashita N, Kawai Y, Tanaka T, Akaike H, Teranishi H, Wakabayashi T, et al. Detection failure rate of chest radiography for the identification of nursing and healthcare-associated pneumonia. J Infect Chemother. 2015;21(7):492–6.
14. Lee KH, Kim WS, Cheon JE, Seo JB, Kim IO, Yeon KM. Squalene aspiration pneumonia in children: radiographic and CT findings as the first clue to diagnosis. Pediatr Radiol. 2005;35(6):619–23.
15. Scheeren B, Gomes E, Alves G, Marchiori E, Hochhegger B. Chest CT findings in patients with dysphagia and aspiration: a systematic review. J Bras Pneumol. 2017;43(4):313–8.
16. Scheeren B, Marchiori E, Pereira J, Meirelles G, Alves G, Hochhegger B. Pulmonary computed tomography findings in patients with chronic aspiration detected by videofluoroscopic swallowing study. Br J Radiol. 2016;89(1063):20160004.
17. Kikuchi R, Watabe N, Konno T, Mishina N, Sekizawa K, Sasaki H. High incidence of silent aspiration in elderly patients with community-acquired pneumonia. Am J Respir Crit Care Med. 1994;150(1):251–3.
18. Matsuse T, Oka T, Kida K, Fukuchi Y. Importance of diffuse aspiration bronchiolitis caused by chronic occult aspiration in the elderly. Chest. 1996;110(5):1289–93.
19. Teramoto S, Yamamoto H, Yamaguchi Y, Tmoita T, Ouchi Y. Diffuse aspiration bronchiolitis due to achalasia. Chest. 2004;125(1):349–50.
20. Hu X, Yi ES, Ryu JH. Diffuse aspiration bronchiolitis: analysis of 20 consecutive patients. J Bras Pneumol. 2015;41(2):161–6.
21. Shimon G, Yonit WW, Gabriel I, Naama BR, Nissim A. The "tree-in-bud" pattern on chest CT: radiologic and microbiologic correlation. Lung. 2015;193(5):823–9.

22. Upchurch CP, Grijalva CG, Wunderink RG, Williams DJ, Waterer GW, Anderson EJ, et al. Community-acquired pneumonia visualized on CT scans but not chest radiographs: pathogens, severity, and clinical outcomes. Chest. 2018;153(3):601–10.
23. Esayag Y, Nikitin I, Bar-Ziv J, Cytter R, Hadas-Halpern I, Zalut T, et al. Diagnostic value of chest radiographs in bedridden patients suspected of having pneumonia. Am J Med. 2010;123(1):88–5.
24. Haga T, Fukuoka M, Morita M, Cho K, Tatsumi K. Computed tomography for the diagnosis and evaluation of the severity of community-acquired pneumonia in the elderly. Intern Med. 2016;55(5):437–41.
25. Seo H, Cha SI, Shin KM, Lim JK, Yoo SS, Lee SY, et al. Community-acquired pneumonia with negative chest radiography findings: clinical and radiological features. Respiration. 2019;97(6):508–17.
26. Haga T, Fukuoka M, Morita M, Cho K, Tatsumi K. Radiographic evaluation of nursing- and healthcare-associated pneumonia. Geriatr Gerontol Int. 2017;17(1):41–7.
27. Vilar J, Domingo ML, Soto C, Cogollos J. Radiology of bacterial pneumonia. Eur J Radiol. 2004;51(2):102–13.
28. Faverio P, Aliberti S, Bellelli G, Suigo G, Lonni S, Pesci A, et al. The management of community-acquired pneumonia in the elderly. Eur J Intern Med. 2014;25(4):312–9.
29. Loubet P, Tubiana S, Claessens YE, Epelboin L, Ficko C, Le Bel J, et al. Community-acquired pneumonia in the emergency department: an algorithm to facilitate diagnosis and guide chest CT scan indication. Clin Microbiol Infect. 2019;26(3):382.
30. Banker PD, Jain VR, Haramati LB. Impact of chest CT on the clinical management of immunocompetent emergency department patients with chest radiographic findings of pneumonia. Emerg Radiol. 2007;14(6):383–8.
31. Varsamas C, Kalkanis A, Gourgoulianis KI. CT versus thoracic ultrasound for discriminating uncomplicated and complicated parapneumonic pleural effusions. Respirology. 2018;23(2):232.
32. Reynolds JH, McDonald G, Alton H, Gordon SB. Pneumonia in the immunocompetent patient. Br J Radiol. 2010;83(996):998–1009.
33. Cardinale L, Parlatano D, Boccuzzi F, Onoscuri M, Volpicelli G, Veltri A. The imaging spectrum of pulmonary tuberculosis. Acta Radiol. 2015;56(5):557–64.
34. Kan T, Komiya K, Honjo K, Uchida S, Goto A, Kawano H, et al. Impact of additional antibiotics on in-hospital mortality in tuberculosis isolated general bacteria: a propensity score analysis. J Infect Chemother. 2019;25(9):714–9.
35. Goto A, Komiya K, Kan T, Honjo K, Uchida S, Takikawa S, et al. Factors associated with atypical radiological findings of pulmonary tuberculosis. PLoS One. 2019;14(7):e0220346.
36. Fujishima N, Komiya K, Matsunaga N, Usagawa Y, Yamasue M, Hashinaga K, et al. A pitfall of treatment with tosufloxacin for pneumonia that might be lung tuberculosis. Intern Med. 2019;58(2):263–6.
37. Reynolds JH, Banerjee AK. Imaging pneumonia in immunocompetent and immunocompromised individuals. Curr Opin Pulm Med. 2012;18(3):194–201.
38. Raju S, Ghosh S, Mehta AC. Chest CT signs in pulmonary disease: a pictorial review. Chest. 2017;151(6):1356–74.
39. Teramoto S, Fukuchi Y, Sasaki H, Sato K, Sekizawa K, Matsuse T. High incidence of aspiration pneumonia in community- and hospital-acquired pneumonia in hospitalized patients: a multicenter, prospective study in Japan. J Am Geriatr Soc. 2008;56(3):577–9.
40. Sun T, Sun L, Wang R, Ren X, Sui DJ, Pu C, et al. Clinical efficacy and safety of moxifloxacin versus levofloxacin plus metronidazole for community-acquired pneumonia with aspiration factors. Chin Med J. 2014;127(7):1201–5.
41. Ito I, Kadowaki S, Tanabe N, Haruna A, Kase M, Yasutomo Y, et al. Tazobactam/piperacillin for moderate-to-severe pneumonia in patients with risk for aspiration: comparison with imipenem/cilastatin. Pulm Pharmacol Ther. 2010;23(5):403–10.

42. Ott SR, Allewelt M, Lorenz J, Reimnitz P, Lode H. Moxifloxacin vs ampicillin/sulbactam in aspiration pneumonia and primary lung abscess. Infection. 2008;36(1):23–30.
43. Kadowaki M, Demura Y, Mizuno S, Uesaka D, Ameshima S, Miyamori I, et al. Reappraisal of clindamycin IV monotherapy for treatment of mild-to-moderate aspiration pneumonia in elderly patients. Chest. 2005;127(4):1276–82.
44. Allewelt M, Schuler P, Bolcskei PL, Mauch H, Lode H. Ampicillin + sulbactam vs clindamycin +/− cephalosporin for the treatment of aspiration pneumonia and primary lung abscess. Clin Microbiol Infect. 2004;10(2):163–70.
45. El Solh A, Okada M, Bhat A, Pietrantoni C. Swallowing disorders post orotracheal intubation in the elderly. Intensive Care Med. 2003;29(9):1451–5.
46. Ishiguro T, Yoshii Y, Kanauchi T, Hoshi T, Takaku Y, Kagiyama N, et al. Re-evaluation of the etiology and clinical and radiological features of community-acquired lobar pneumonia in adults. J Infect Chemother. 2018;24(6):463–9.
47. Brewin A, Arango L, Hadley WK, Murray JF. High-dose penicillin therapy and pneumococcal pneumonia. JAMA. 1974;230(3):409–13.
48. Okada F, Ando Y, Matsushita S, Ishii R, Nakayama T, Morikawa K, et al. Thin-section CT findings of patients with acute *Streptococcus pneumoniae* pneumonia with and without concurrent infection. Br J Radiol. 2012;85(1016):e357–64.
49. Morikawa K, Okada F, Ando Y, Ishii R, Matsushita S, Ono A, et al. Methicillin-resistant *Staphylococcus aureus* and methicillin-susceptible *S. aureus* pneumonia: comparison of clinical and thin-section CT findings. Br J Radiol. 2012;85(1014):e168–75.
50. Jenkins A, Diep BA, Mai TT, Vo NH, Warrener P, Suzich J, et al. Differential expression and roles of *Staphylococcus aureus* virulence determinants during colonization and disease. mBio. 2015;6(1):e02272–14.
51. Navon-Venezia S, Kondratyeva K, Carattoli A. *Klebsiella pneumoniae*: a major worldwide source and shuttle for antibiotic resistance. FEMS Microbiol Rev. 2017;41(3):252–75.
52. Ashurst JV, Dawson A. Klebsiella pneumonia. Treasure Island (FL): StatPearls; 2019.
53. DiBardino DM, Wunderink RG. Aspiration pneumonia: a review of modern trends. J Crit Care. 2015;30(1):40–8.
54. Steele CM, Cichero JA. Physiological factors related to aspiration risk: a systematic review. Dysphagia. 2014;29(3):295–304.
55. Schmidt AJ, Stark P. Radiographic findings in Klebsiella (Friedlander's) pneumonia: the bulging fissure sign. Semin Respir Infect. 1998;13(1):80–2.
56. Ruiz LA, Zalacain R, Gomez A, Camino J, Jaca C, Nunez JM. *Escherichia coli*: an unknown and infrequent cause of community acquired pneumonia. Scand J Infect Dis. 2008;40(5):424–7.
57. Jaffey PB, English PW 2nd, Campbell GA, Rubin SA, Haque AK. *Escherichia coli* lobar pneumonia: fatal infection in a patient with mental retardation. South Med J. 1996;89(6):628–30.
58. Leung JM, Tiew PY, Mac Aogain M, Budden KF, Yong VF, Thomas SS, et al. The role of acute and chronic respiratory colonization and infections in the pathogenesis of COPD. Respirology. 2017;22(4):634–50.
59. Pearlberg J, Haggar AM, Saravolatz L, Beute GH, Popovich J. Hemophilus influenzae pneumonia in the adult. Radiographic appearance with clinical correlation. Radiology. 1984;151(1):23–6.
60. Fujitani S, Sun HY, Yu VL, Weingarten JA. Pneumonia due to *Pseudomonas aeruginosa*: part I: epidemiology, clinical diagnosis, and source. Chest. 2011;139(4):909–19.
61. Lund-Palau H, Turnbull AR, Bush A, Bardin E, Cameron L, Soren O, et al. *Pseudomonas aeruginosa* infection in cystic fibrosis: pathophysiological mechanisms and therapeutic approaches. Expert Rev Respir Med. 2016;10(6):685–97.
62. Finch S, McDonnell MJ, Abo-Leyah H, Aliberti S, Chalmers JD. A comprehensive analysis of the impact of *Pseudomonas aeruginosa* colonization on prognosis in adult bronchiectasis. Ann Am Thorac Soc. 2015;12(11):1602–11.

63. Wilson R, Aksamit T, Aliberti S, De Soyza A, Elborn JS, Goeminne P, et al. Challenges in managing *Pseudomonas aeruginosa* in non-cystic fibrosis bronchiectasis. Respir Med. 2016;117:179–89.
64. Winer-Muram HT, Jennings SG, Wunderink RG, Jones CB, Leeper KV Jr. Ventilator-associated *Pseudomonas aeruginosa* pneumonia: radiographic findings. Radiology. 1995;195(1):247–52.
65. Bartlett JG, O'Keefe P, Tally FP, Louie TJ, Gorbach SL. Bacteriology of hospital-acquired pneumonia. Arch Intern Med. 1986;146(5):868–71.
66. Bartlett JG. How important are anaerobic bacteria in aspiration pneumonia: when should they be treated and what is optimal therapy. Infect Dis Clin N Am. 2013;27(1):149–55.
67. Landay MJ, Christensen EE, Bynum LJ, Goodman C. Anaerobic pleural and pulmonary infections. AJR Am J Roentgenol. 1980;134(2):233–40.

Chapter 5
Assessment of Swallowing Function and Dysphagia: Is the Assessment of Swallowing Function Necessary for the Diagnosis of Aspiration Pneumonia?

Yoshihiro Suido and Shinji Teramoto

Abstract Microaspiration during the night, i.e., silent aspiration, is a major mechanism of aspiration pneumonia (AP) in elderly patients. Thus, swallowing abnormalities such as dysphagia are major risk factors for the development of AP. Dysphagia is an important upper airway disorder causing respiratory tract illnesses. We must always be aware of the possibility that severe dysphagia patients may develop a variety of pulmonary diseases. To assess AP risks and conduct therapeutic strategy for AP, assessment of swallowing function is necessary in many clinical settings. Methods for assessing dysphagia range from bedside assessments by speech therapists to videofluoroscopic examinations of swallowing by physicians. Videofluoroscopic and/or videoendoscopic swallowing studies may be used to determine the nature and extent of swallow disorders. In frail elderly patients who require a comprehensive nursing care, videofluoroscopic examination of swallowing is not recommended. Bedside swallowing function assessments including simple swallowing provocation tests and oximeter monitoring are safely performed.

Keywords Silent aspiration · Dysphagia · Swallowing reflex · Simple swallowing provocation tests · Videofluoroscopic examination · Pneumonia

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1 Introduction

Aspiration pneumonia (AP) is often found in elderly, debilitated patients with dysphagia. Since microaspiration during the night, i.e. silent aspiration, is a major mechanism of AP in elderly patients, swallowing abnormality such as dysphagia is a crucial risk factor for the development of AP [1–4]. Swallowing movement is primarily intended to obtain food and nourishment in humans. Because the pharynx is a shared conduit for swallowing and respiration, it is known that the breathing cycle is well coordinated with swallowing in humans [5, 6]. Thus, normal swallowing also protects the respiratory tracts from untoward aspiration. On the other hand, dysphagia may be an important upper airway disorder affecting respiratory tract illnesses. We must always be aware of the possibility that severe dysphagia patients may develop a variety of pulmonary diseases including AP [7–11]. To assess AP risks and conduct therapeutic strategy for AP, assessment of swallowing function is necessary in many clinical settings. Screening tests for dysphagia are intended to select patients who are strongly suspected of dysphagia [12, 13]. In this chapter, we described the methods of assessment of swallowing function in healthy and patients with the risk of AP.

2 Assessment of Swallowing Function Is Necessary for the Diagnosis of Aspiration Pneumonia

The definition of AP is clearly determined by the Japanese Respiratory Society (JRS) guidelines for the management of nursing and healthcare-associated pneumonia and HAP in adults [14, 15]. According to these guidelines, AP should be diagnosed as pneumonia that develops in patients in whom dysphagia and aspiration is known to occur (or is strongly suspected) (Table 5.1) [14].

Both apparent and silent aspirations and their related systemic disorders are recognized as pivotal risk factors for the development of AP. It is important to conduct swallowing function tests as a means of detecting swallowing abnormality and to determine whether aspiration has occurred during and after meals. Methods of testing for dysphagia range from simple bedside assessments to more detailed videofluoroscopic (VF) examinations of swallowing (Table 5.2) [15].

3 Evidences of Aspiration Pneumonia, but not Aspiration Pneumonitis, Being Not Caused by Food and Water Aspiration

In elderly patients, AP occurs as a consequence of frequent silent aspiration. The silent aspiration of oropharyngeal contents including bacteria during the night cause small inflammation in lower respiratory tracts, resulting in the insidious

Table 5.1 Pathological conditions that predispose to aspiration (partial revision of the first edition of *the JRS Guidelines for the Management of Hospital-Acquired Pneumonia in Adults*)

1. Neurological disorders Cerebrovascular disease (acute phase, chronic phase) Central neurodegenerative diseases Parkinson's disease Dementia (cerebrovascular, Alzheimer's type)
2. Bedriddenness (regardless of disease)
3. Oral disorders Dental occlusion disorders (including ill-fitting dentures) Dry mouth Oral malignant tumors
4. Gastroesophageal disorders Esophageal diverticula Esophageal motility disorders (achalasia, scleroderma) Malignant tumors Gastroesophageal reflux disorders (including esophageal hiatal hernia) Gastrectomy (total or subtotal gastrectomy)
5. Iatrogenic causes Sedatives, hypnotics Drugs that cause dry mouth, e.g., anticholinergic drugs Tube feeding

Table 5.2 Procedures for detection of functional dysphagia

1. Screening Methods Chest X-ray Bedside assessment of swallowing function Cervical auscultation of swallowing Arterial oxygen saturation monitoring during swallowing Repetitive saliva swallowing test (RSST), Water swallowing test (WST), Simple swallowing provocation test (SSPT), etc.
2. Further Swallowing Assessment Methods Chest CT examination Modified Water swallowing test (MWST), Videofluoroscopic examination of swallowing, Videoendoscopic examination of swallowing, Laryngoscopic evaluation of swallowing, Swallowing pressure measurement, Simple two-step swallowing provocation test, Swallowing provocation test (SPT), Examination of pulmonary uptake of a radioisotope, such as indium chloride, dissolved in the mouth the previous night

development of bacterial pneumonia. In this process, food aspiration during daytime is not relevant. There are evidences of AP, but not aspiration pneumonitis, being not caused by food and water aspiration. There are plenty of evidences that acid aspiration and water aspiration do not cause pneumonia in humans and animals.

3.1 Chronic Food Aspiration-Related Respiratory Bronchiolitis Such as Diffuse Aspiration Bronchiolitis Is Not Associated with the Risk of AP

Diffuse aspiration bronchiolitis (DAB) is defined as a clinical entity that is characterized by chronic inflammation of bronchioles caused by recurrent aspiration of foreign materials [8–10]. The onset of DAB was more insidious than aspiration pneumonia, and in half of the patients with DAB, episodes of aspiration were unrecognized. Although some of the patients with AP were dead in spite of proper treatment, the prognosis of DAB is usually good. That is why food aspiration may cause a type of pneumonitis, but does not always cause serious pneumonia in the elderly. In some cases, fungi-y flora staining, which is specific to fungi or vegetables, revealed the insidious low-grade lung inflammation caused by food materials [8–10]. The clinical course of DAB implies that the aspiration of food material alone does not cause severe pneumonia [9, 16].

3.2 HCl Instillation Animal Model Did Not Cause the Similar Pathology of AP

There are many AP animal models using applying exogenous insults. HCL is one of the most frequent insults applied to the lower lungs. In our experiences, an animal model by administering HCl intratracheally to rats every 2 days for 2 weeks does not cause pneumonia [17]. There is no increase in lung free cells, TNFα-production, and elastase-like activity in this animal model. Further, acute lung injury induced by acid aspiration of 2 mL/kg HCl (pH = 1.5) was rarely observed in control mice, but frequently observed in mice with a disrupted cytosolic phospholipase A2 (*cPLA2*) gene [18]. It has recently reported that 2.5 mL/kg of intra-bronchial HCl produced substantial yet sublethal acute lung injury in mice, but lower doses of HCl did not result in reproducible and homogenous lung injury [19].

3.3 Massive Gastric Content Aspiration Such as Mendelson's Syndrome Is Different from a Typical AP

Aspiration of gastric contents induces not only severe pneumonitis but also damages the airway. This condition was determined as a Mendelson's syndrome [20]. Mendelson's syndrome is chemical pneumonitis or aspiration pneumonitis caused by aspiration during anesthesia, especially during pregnancy. The condition is severe pneumonitis, but not bacterial pneumonia like AP. The underlying pathobiology is characterized by an excessive inflammatory response. The lung can be injured directly, such as in pneumonia or with gastric acid aspiration, or indirectly [21]. The

condition is closely related to acute respiratory distress syndrome (ARDS). Following the initial insult, ARDS pathogenesis progresses in three phases: exudative, proliferative, and fibrotic phase 1. These phases are characterized by distinct molecular and cellular immune and repair mechanisms that determine the prognosis of ARDS [22].

4 Conditions and Underlying Disorders Likely to Cause Dysphagia

AP is mainly caused by miss-swallowing of foreign substances, so dysphagia patients and underlying conditions that cause swallowing difficulties need to be well understood. During early stages of dysphagia, choking caused by aspiration is a conspicuous symptom that can be noticed objectively. Choking is a result of protective reflex induced by the entry of a food bolus into the trachea. In contrast, apparent aspiration in the chronic phase is not seen in most cases, while silent aspiration is almost certainly occurring. The silent aspiration is frequently seen in elderly patients, in particular during the night.

The most frequent underlying disorders likely to cause dysphagia is an acute or a previous cerebral infarction (Table 5.3). In the acute phase, apparent aspiration is the main form, and silent aspiration also occurs continually [23–25]. Since there is an age-related change in muscle function and neurological function, old age itself is a risk factor for dysphagia [26, 27]. Although the swallowing reflex does not decline with aging alone, the delays or declines in the swallowing reflex are frequently observed in the elderly. In age-related anatomical alterations, the position of the larynx is often seen to shift to a lower position in the neck. Saliva secretions are also known to decease with age. Patients with neuromuscular disease including ALS, Parkinson's disease, and dermatomyositis are also susceptible to apparent as well as silent aspiration. Impaired swallowing function and decreased cough reflex have been reported in patients with Parkinson's disease [28–30]. Sleep also suppresses neuron projection in the upper airway reflex from the brain, along with cough and swallowing reflexes [31–34]. In the end, microaspiration occurs frequently during the night. Likewise, sedatives, sleeping pills, and psychotropic agents cause decline in the swallowing reflex via projection pathways or muscle relaxation effects, producing aspiration [35–40].

Aspiration also occurs in patients who have undergone gastrectomy. Gastrectomy inhibits the function of lower esophageal sphincters, resulting in reflux from the stomach and aspiration of gastric contents. Nasogastric tubing or tracheal cannulation is also a risk factor for AP [41–43]. In nasogastric tube patients, reflux to the pharynx occurs during the night with the gastric tube acting as a conduit, and reflux material accumulated in the pharynx is repeatedly aspirated. The tracheal cannula itself interferes with laryngeal elevation and facilitates microaspiration.

Table 5.3 Conditions with possible swallowing function disorder

• Positive results of screening swallowing function tests
• old age (elderly patients)
• previous or acute cerebrovascular disorder
• neurodegenerative disorder and neuromuscular disease
• impaired consciousness, cognition disorder (dementia)
• gastroesophageal reflux, gastrectomy (particularly total gastrectomy)
• laryngeal, pharyngeal tumor
• tracheotomy with cuffed tube, nasogastric tube replacement
• muscle weakness, sarcopenia
• nutritional impairment, cachexia
• poly-pharmacy
• nursing home residency
• chronic respiratory diseases (COPD, old tuberculosis sequela)
• sleep disordered breathing (OSAS)
• chronic heart diseases (chronic heart failure)
• poor trunk support that cannot maintain a sitting position for long
• poor oral health-care or ill-fitting dentures

5 Swallowing Function Assessments in Terms of Detecting AP Risk

The VF and videoendoscopic (VE) examination of swallowing are the gold standards at this time for the assessment of the whole swallowing function. However, these methods may not be suitable for detecting AP risks. Since food aspiration and water aspiration do not generally cause AP, silent aspiration during the night is the main mechanism of AP in older adults.

Until now, many tests are variable for the assessment of swallowing function in a variety of patients. Highly sensitive tests and simple screening tests that lead to these examinations are useful when examining general outpatients, inpatients at the bedside, and in-home care patients. When performed on elderly patients who require a high level of nursing care, VF examinations of swallowing that are performed with the patient seated may result in aspiration during or after the examination, and priority should therefore be given to procedures such as bedside swallowing function assessments and simple swallowing provocation tests [44, 45]. These examinations should be performed in accordance with the healthcare environment at each nursing care facility.

The most definite examination of silent aspiration is the special approach using radioisotope techniques. We can identify the radiolabeled solution in gauze and fixed to the subject's teeth before night is aspirated into either trachea or esophagus in humans [46]. Although the method is scientific and it is a definite way to

determine silent aspiration during the night, the examination is not applied for patients in clinical settings due to ethical reasons. Table 5.2 shows the list of criteria for selecting patients with high risk of dysphagia, which is usually performed by physicians in Japan.

5.1 Procedures for Simple Screening Tests

Prior to assessing the swallowing function in patients with possible dysphagia, the diagnostic procedure for dysphagia starts with collecting patient information through history-taking, visual examination, chest X ray, and Chest CT examination. Patients suspected with dysphagia proceed to the screening tests listed in Table 5.2. Based on test results, high-risk patients who are reasonably suspected of having dysphagia are screened, and if necessary, these patients proceed to more thorough examination such as VF or VE examinations of swallowing. Several screening methods without endoscopy are performed by physicians of other specialties or speech therapists. When using any of the following methods in practice, one should make a comprehensive judgment without insisting on anyone particular method.

5.1.1 Saliva Swallowing (Repetitive Saliva Swallowing Test (RSST))

Humans repeat swallowing at certain intervals in order to dispose of saliva in the mouth, even when not eating. This dry swallowing is the basic movement used to dispose of saliva [47]. Repetitive saliva swallowing test (RSST) is intended to check the patient's ability to voluntarily swallow repeatedly. RSST is simple and also relatively safe to conduct [48, 49]. Three or more dry swallows within 30 s is considered normal. The number of swallows is counted by the movement of laryngeal elevation, either visually or by palpating.

5.1.2 Water Swallowing Test (WST)

Water is difficult to swallow for patients with dysphagia, especially in patients with static dysphagia with poor food transport function due to cerebrovascular or neuromuscular disease. This test is intended to detect aspiration with high accuracy by having the patient swallow water [44, 50]. According to the original method as proposed by Kubota et al., 33 mL of water should be used in the first attempt, followed by an additional 30 mL (Table 5.4). However, since 30 mL of water poses greater risk for patients at risk of aspiration, it has recently been reduced to 3 mL of water with close monitoring of the patient's condition. Similar tests that use custard pudding or jelly to evaluate swallowing function also exist.

Table 5.4 Procedure for water swallowing tests

[Procedure]
The patient is asked to sit on a chair and is handed a cup containing 30 mL of water at normal temperature. The patient is then asked to "please drink this water as you usually do." Time to empty a cup is measured, and the drinking profile and episodes are monitored and assessed.
[Drinking profile]
1. The patient can drink all the water in 1 gulp without choking.
2. The patient can drink all the water in 2 or more gulps without choking.
3. The patient can drink all the water in 1 gulp, but with some choking.
4. The patient can drink all the water in 2 or more gulps, but with some choking.
5. The patient often chokes and has difficulty drinking all the water.
[Drinking episodes]
Sipping, holding water in the mouth while drinking, water coming out of the mouth, a tendency to try to force himself/herself to continue drinking despite choking, drinking water in a cautious manner, etc.
[Diagnosis]
Normal: Completed profile #1 within 5 s
Suspected: Completed profile #1 in more than 5 s, or profile #2
Abnormal: Any cases of profiles #3 through 5

5.1.3 Cervical Auscultation of Swallowing

Cervical auscultation during or after swallowing allows noninvasive assessment of aspiration or the presence of residual food in the pharynx [51, 52]. Changes in breathing sound (mostly expiratory sound) and presence of a respiratory murmur in the pharynx after swallowing are particularly important in the assessment, such as moist sound, stenotic sound, wheezing, gargling sound, and liquid vibrating sound. There have been studies on swallowing sound that can be heard for a short time during swallowing.

5.1.4 Arterial Oxygen Saturation Monitoring During Swallowing

This method uses a pulse oximeter to monitor arterial oxygen saturation (SpO_2) during meals to infer potential aspiration from decreased SpO_2. In practice, the patient should be instructed to discontinue a meal if subject SpO_2 decreases to 90% or lower or by an average of 3% per minute from the baseline when eating [53, 54]. Although this test does not directly detect aspiration, it is useful in monitoring breathing condition during meals as risk management. However, it has been suggested that aspiration occurring on VF swallowing study (VFSS) cannot be predicted based on decrease in SpO_2 in pulse oximetry [55]. The application of pulse oximetry to detect aspiration during regular meals requires further investigation.

Table 5.5 Method of assessing swallowing by simple swallowing test

Step 1: Inject 0.4 mL of distilled water, and observe the patient for 3 s
Assessment of 'swallowing reflex (+)' there is no or little risk of aspiration pneumonia assessment of "swallowing reflex(−)" proceed to step 2
Step 2: Inject 2 mL of distilled water, and observe the patient for 3 s
Assessment of "swallowing (−)" or "aspiration (+)" there is a high risk of aspiration pneumonia

5.1.5 Plain X-Ray of the Neck

The patient is asked to swallow a small volume of contrast medium. By comparing plain X-ray images of the neck taken before and after the swallowing, conditions of laryngeal influx and the presence of aspiration or pharyngeal residue can be found. Unlike X-ray fluoroscopy, this method does not allow dynamic monitoring of swallowing; however, it can be conducted easily using ordinary X-ray equipment.

5.1.6 Swallowing Provocation Test (SPT; Swallowing Reflex Test) (Table 5.5)

This method uses a thin tube inserted through the nose into the oropharynx area followed by injection of a small volume of water in order to measure the time from injection to start of swallowing reflex. The average reflex time in healthy individuals of older adults was 1.7 s when using 0.4 mL of distilled water at normal temperature, and 3 s or longer is considered abnormal [44, 45]. This test allows the assessment of sensory input and motor output in the pharynx in the absence of influence of the oral phase and therefore can assess the risk of silent aspiration. This method requires some experience of tube insertion. In acute stroke patients with an impairment of the pharyngeal phase of swallowing, first-step SPT reliably detects aspiration risk [56]. This test is also modified to endoscopic swallowing test as SPT with fiberoptic endoscopic evaluation of swallowing (FEES). The test is a useful examination for dysphagia rehabilitation [57].

5.2 VFSS and FEES

VFSS and FEES are the two most commonly used instrumental swallowing assessment techniques [58–62]. While both tools rely on perceptual judgements by the assessing clinician, they are recognized as complementary best clinical standards with acceptable levels of inter and intra-rater reliability [58]. Both tools allow the clinician to trial different food textures, fluid viscosities, compensatory postures,

swallowing maneuvers, and methods of food/fluid presentation to investigate dysphagia presence, profile and the impact of intervention.

5.2.1 An Example of VFSS Examination Protocol

During the VF protocol, each participant self-fed 12 barium boluses (via 30-mL medicine cups) under fluoroscopy [63]. Boluses included 3 × 5 mL "ultrathin" liquid barium, 3 × 20 mL "ultrathin" liquid barium, and 3 × 5 mL nectar-thick barium. Three additional 5-mL nectars were swallowed using the "Effortful Swallow" maneuver and are not included in this analysis. The order of bolus administration was not randomized for the following reasons: small volumes of thin liquid were administered first to minimize potential risk of large-volume aspiration, and nectar was provided last to prevent potential residue from thicker boluses from contaminating other trials. Each medicine cup contained 1 mL more than the target volume (measured by syringe) to control for the residual barium left in the cup [64]. "Ultrathin" barium was made by taking Varibar (Bracco Imaging) thin liquid and diluting it by 50% with water. This concentration of barium (20% w/v) has been shown to be more sensitive to aspiration than traditional 40% w/v Varibar (40% w/v) [65].

5.2.2 An Example of FEES Examination Protocol

During the FEES examination, the participants were offered three trials of thin and three trials of thick liquid followed by one small bite-sized cracker (making a total of seven swallow trials). Each liquid trial contained 10 mL of water or applesauce and was dyed with 5% methylene blue. The tip of the flexible fiberoptic endoscope was positioned just above the epiglottis in what is called the high position [66]. FEES images were obtained using a camera, a light source, and a computerized video archiving system and recorded on a DVD. Neither a nasal vasoconstrictor nor a topical anesthetic had been administered to the nasal mucosa.

6 Conclusion

Diagnosis of dysphagia begins with suspecting its presence, and then patients with high risk must be selected using simple screening tests, including those described in this paper. Many of these tests are relatively easy to perform and are extremely useful in obtaining a rough picture of the swallowing condition. To assess the AP risk and conduct therapeutic strategy for AP, assessment of swallowing function is necessary in many clinical settings. Methods for testing dysphagia range from bedside assessments by speech therapists to VF examinations of swallowing by physicians. VF and/or VE swallowing studies may be used to determine the nature and extent of

any swallowing disorder. In frail elderly patients who require a comprehensive nursing care, VF examination of swallowing is not recommended. The bedside swallowing function assessments including simple swallowing provocation tests and oximeter monitoring are safely performed.

References

1. Marik PE. Aspiration pneumonitis and aspiration pneumonia. N Engl J Med. 2001;344(9):665–71.
2. Mandell LA, Niederman MS. Aspiration pneumonia. N Engl J Med. 2019;380:651–63.
3. Teramoto S, Fukuchi Y, Sasaki H, Sato K, Sekizawa K, Matsuse T, Japanese Study Group on Aspiration Pulmonary Disease. High incidence of aspiration pneumonia in community- and hospital-acquired pneumonia in hospitalized patients: a multi-center, prospective study in Japan. J Am Geriatr Soc. 2008;56:577–9.
4. Teramoto S, Kawashima M, Komiya K, Shoji S. Health care-associated pneumonia may be primary due to aspiration pneumonia. Chest. 2009;136:1702–3.
5. Paydarfar D, Gilbert RJ, Poppel CS, et al. Respiratory phase resetting and airflow changes induced by swallowing in humans. J Physiol Lond. 1995;483:273–88.
6. Leopold NA, Kagel MC. Swallowing, ingestion and dysphagia: a reappraisal. Arch Phys Med Rehabil. 1983;64:371–3.
7. Teramoto S. Novel preventive and therapeutic strategy for post-stroke pneumonia. Post-stroke pneumonia. Expert Rev Neurother. 2009;9:1187–200.
8. Teramoto S. Clinical significance of aspiration pneumonia and diffuse aspiration bronchiolitis in the elderly. J Gerontol Geriat Res. 2014;3:142. https://doi.org/10.4172/2167-7182.1000142.
9. Matsuse T, Oka T, Kida K, Fukuchi Y. Importance of diffuse aspiration bronchiolitis caused by chronic occult aspiration in the elderly. Chest. 1996;110:1289–93.
10. Matsuse T, Teramoto S, Matsui H, Ouchi Y, Fukuchi Y. Widespread occurrence of diffuse aspiration bronchiolitis in patients with dysphagia, irrespective of age. Chest. 1998;114:350–1.
11. Teramoto S, Ishii T, Yamamoto H, et al. Significance of chronic cough as a defence mechanism or a symptom in elderly patients with aspiration and aspiration pneumonia. Eur Respir J. 2005;25:210–1.
12. Teramoto S, Yamamoto H, Yamaguchi Y, Ouchi Y, Matsuse T. A novel diagnostic test for the risk of aspiration pneumonia in the elderly. Chest. 2004;125(2):801–2.
13. Teramoto S, Ishii T, Matsuse T, Fukuchi Y. Use of a new tool and detection of aspiration in decision-making for safe feeding after stroke. Age Ageing. 2001;30:527–34.
14. Aspiration pneumonia. The committee for The Japanese respiratory society guidelines in management of respiratory infections. Respirology. 2004;9:S35–7.
15. The committee for the Japanese Respiratory Society in the management of Nursing and Healthcare-associated pneumonia. Guidelines for the management of Nursing and Healthcare-associated pneumonia. Tokyo: The Japanese Respiratory Society; 2011.
16. Shimada M, Teramoto S, Mastui H, Tamura A, Akagawa S, et al. Nine pulmonary aspiration syndrome cases of atypical clinical presentation, in which the final diagnosis was obtained by histological examinations. Respir Investig. 2014;52:14–20.
17. Sudo E, Fukuchi Y, Ishida K, et al. Diffuse aspiration bronchiolitis (DAB) produced in animals by repeated HCl microaspiration. Jpn J Geriat. 1994;31:435–40. (in Japanese)
18. Nagase T, Uozumi N, Ishii S, Kume K, Izumi T, Ouchi Y, Shimizu T. Acute lung injury by sepsis and acid aspiration: a key role for cytosolic phospholipase A2. Nat Immunol. 2000;1(1):42–6.
19. Tavares AH, Colby JK, Levy BD, Abdulnour RE. A model of self-limited acute lung injury by unilateral intra-bronchial acid instillation. J Vis Exp. 2019;150:e60024. https://doi.org/10.3791/60024.

20. Mendelson CL. The aspiration of stomach contents into the lungs during obstetric anesthesia. Am J Obstet Gynecol. 1946;52:191205.
21. Baron RM, Levy BD, et al. Acute respiratory distress syndrome. In: Jameson JL, editor. Harrison's principles of internal medicine. New York: McGraw-Hill Education; 2018.
22. Thompson BT, Chambers RC, Liu KD. Acute respiratory distress syndrome. N Engl J Med. 2017;377:562–72.
23. Vermeij FH, Scholte O, Reimer WJ, de Man P, et al. Stroke-associated infection is an independent risk factor for poor outcome after acute ischemic stroke: data from the Netherlands stroke survey. Cerebrovasc Dis. 2009;27:465–71.
24. Bravata DW. Pneumonia most common reason for readmission after stroke. Stroke. 2007;38:1899–904.
25. Martino R, Foley N, Bhogal S, Diamant N, Speechley M, Teasell R. Dysphagia after stroke: incidence, diagnosis, and pulmonary complications. Stroke. 2005;36:2756–63.
26. Daniels SK, Brailey K, Priestly DH, Herrington LR, Weisberg LA, Foundas AL. Aspiration in patients with acute stroke. Arch Phys Med Rehabil. 1998;79:14–9.
27. Ramsey D, Smithard D, Kalra L. Silent aspiration: what do we know? Dysphagia. 2005;20:218–25.
28. Lin CW, Chang YC, Chen WS, Chang K, Chang HY, et al. Prolonged swallowing time in dysphagic parkinsonism patients with aspiration pneumonia. Arch Phys Med Rehabil. 2012;93:2080–4.
29. Sorenson EJ, Crum B, Stevens JC. Incidence of aspiration pneumonia in ALS in Olmsted County, MN. Amyotroph Lateral Scler. 2007;8(2):87–9.
30. Mugii N, Hasegawa M, Matsushita T, Hamaguchi T, Oohata S, Okita H, et al. Oropharyngeal dysphagia in dermatomyositis: associations with clinical and laboratory features including autoantibodies. PLoS One. 2016;11(5):e0154746.
31. Pontopiddan H, Beecher HK. Progressive loss of protective reflexes in the airway with the advancing age. JAMA. 1960;174:2209–13.
32. Yoshikawa M, Yoshida M, Nagasaki T, Tanimoto K, Tsuga K, Akagawa Y. Influence of aging and denture use on liquid swallowing in healthy dentulous and edentulous older people. J Am Geriatr Soc. 2006;54:444–9.
33. Baijens LW, Speyer R. Effects of therapy for dysphagia in Parkinson's disease: systematic review. Dysphagia. 2009;24:91–102.
34. Widdicombe J, Singh V. Physiological and pathophysiological down-regulation of cough. Respir Physiol Neurobiol. 2006;150(2–3):105–17.
35. Teramoto S, Ishii T, Matsuse T. Relationship between swallowing function and gas exchange during day and night in patients with obstructive sleep apnea syndrome. Dysphagia. 2001;16(4):249–53.
36. Pasricha PJ. Effect of sleep on gastroesophageal physiology and airway protective mechanisms. Am J Med. 2003;115(Suppl. 3A):S114–8.
37. Wyllie E, Wyllie R, Cruse RP, Rothner AD, Erenberg G. The mechanism of nitrazepam-induced drooling and aspiration. N Engl J Med. 1986;314:35–8.
38. Nishino T, Takizawa K, Yokokawa N, Hiraga K. Depression of the swallowing reflex during sedation and/or relative analgesia produced by inhalation of 50% nitrous oxide in oxygen. Anesthesiology. 1987;67(6):995–8.
39. Teramoto S, Matsui H, Ohga E, Ishii T, Matsuse T, Ouchi Y. A novel model of aspiration in young and old Guinea-pigs using LacZ gene transduction of adenovirus vector. Br J Anaesth. 1999;83:296–301.
40. Teramoto S, Matsuse T, Oka T, Ito H, Fukuchi Y, Ouchi Y. Investigation of effects of anesthesia and age on aspiration in mice through LacZ gene transfer by recombinant E1-deleted adenovirus vectors. Am J Respir Crit Care Med. 1998;158:1914–9.
41. Marumo K, Homma S, Fukuchi Y. Postgastrectomy aspiration pneumonia. Chest. 1995;107:453–6.

42. Ferrer M, Bauer TT, Torres A, Hernandez C, Piera C. Effect of nasogastric tube size on gastroesophageal reflux and microaspiration in intubated patients. Ann Intern Med. 1999;130:991–4.
43. Teramoto S, Ishii T, Yamamoto H, Yamaguchi Y, Ouchi Y. Nasogastric tube feeding is a cause of aspiration pneumonia in ventilated patients. Eur Respir J. 2006;27(2):436–7.
44. Teramoto S, Fukuchi Y. Detection of aspiration and swallowing disorder in older stroke patients: simple swallowing provocation test versus water swallowing test. Arch Phys Med Regabil. 2000;81(11):1517–9.
45. Teramoto S, Matsuse T, Fukuchi Y, Ouchi Y. Simple two-step swallowing provocation test for elderly patients with aspiration pneumonia. Lancet. 1999;353(9160):1243.
46. Kikuchi R, Watabe N, Konno T, Mishina N, Sekizawa K, Sasaki H. High incidence of silent aspiration in elderly patients with community-acquired pneumonia. Am J Respir Crit Care Med. 1994;150(1):251–3.
47. Persson E, Wårdh I, Östberg P. Repetitive saliva swallowing test: norms, clinical relevance and the impact of saliva secretion. Dysphagia. 2019 Apr;34(2):271–8.
48. Cheng YM, Lan SH, Hsieh YP, Lan SJ, Hsu SW. Evaluate five different diagnostic tests for dry mouth assessment in geriatric residents in long-term institutions in Taiwan. BMC Oral Health. 2019;19(1):106.
49. Watanabe S, Oh-Shige H, Oh-Iwa I, Miyachi H, Shimozato K, Nagao T. Reconsideration of three screening tests for dysphagia in patients with cerebrovascular disease performed by non-expert examiners. Odontology. 2019;108:117. https://doi.org/10.1007/s10266-019-00431-9.
50. Kubota T, Mishima H, Hanada M, et al. Paralytic dysphagia incerebrovascular disorder; screening tests and their clinical application. Gen Rehabil. 1982;10:271–6. (in Japanese)
51. Nozue S, Ihara Y, Takahashi K, Harada Y, Takei Y, Yuasa K, Yokoyama K. Accuracy of cervical auscultation in detecting the presence of material in the airway. Clin Exp Dent Res. 2017;3(6):209–14.
52. Kurosu A, Coyle JL, Dudik JM, Sejdic E. Detection of swallow kinematic events from acoustic high-resolution cervical auscultation signals in patients with stroke. Arch Phys Med Rehabil. 2019 Mar;100(3):501–8.
53. Chapman KR, Rebuck AS. Dysphagia as a manifestation of occult hypoxemia. The role of oximetry during meal times. Chest. 1991;99(4):1030–2.
54. Sherman B, Nisenboum JM, Jesberger BL, et al. Assessment of dysphagia with the use of pulse oximetry. Dysphagia. 1999;14:152–6.
55. Wang TG, Chang YC, Chen SY, Hsiao TY. Pulse oximetry does not reliably detect aspiration on videofluoroscopic swallowing study. Arch Phys Med Rehabil. 2005;86(4):730–4.
56. Warnecke T, Teismann I, Meimann W, Olenberg S, Zimmermann J, Krämer C, Ringelstein EB, Schäbitz WR, Dziewas R. Assessment of aspiration risk in acute ischaemic stroke - evaluation of the simple swallowing provocation test. J Neurol Neurosurg Psychiatry. 2008;79(3):312–4.
57. Tejima C, Kikutani T, Takahashi N, Tamura F, Yoshida M. Application of simple swallowing provocation test with fiberoptic endoscopic evaluation of swallowing in a cross-sectional study. BMC Geriatr. 2015;15:48. https://doi.org/10.1186/s12877-015-0049-5.
58. Langmore SE. History of fiberoptic endoscopic evaluation of swallowing for evaluation and management of pharyngeal dysphagia: changes over the years. Dysphagia. 2017;32(1):27–38.
59. Rao N. Gold-standard? Analysis of the videofluoroscopic and fiberopting endoscopic swallow examinations. J Appl Res. 2003;3(1):89–96.
60. Kelly Annette M, Drinnan Michael J, Leslie P. Assessing penetration and aspiration: how do videofluoroscopy and fiberoptic endoscopic evaluation of swallowing compare? Laryngoscope. 2009;117(10):1723–7.
61. Pisegna JM, Langmore SE. Parameters of instrumental swallowing evaluations: describing a diagnostic dilemma. Dysphagia. 2016;31(3):462–72.
62. Peladeau-Pigeon M, Steele CM. Technical aspects of a videofluoroscopic swallowing study. CJSLPA. 2013;37(3):216–2.

63. Molfenter SM, Brates D, Herzberg E, Noorani M, Lazarus C. The swallowing profile of healthy aging adults: comparing noninvasive swallow tests to videofluoroscopic measures of safety and efficiency. J Speech Lang Hear Res. 2018;61(7):1603–12. https://doi.org/10.1044/2018_JSLHR-S-17-0471.
64. Molfenter SM, Steele CM. Variation in temporal measures of swallowing: sex and volume effects. Dysphagia. 2013;28(2):226–33.
65. Fink TA, Ross JB. Are we testing a true thin liquid? Dysphagia. 2009;24(3):285–9.
66. Langmore SE, Aviv JE. Endoscopic evaluation and treatment of swallowing disorders. New York: Thieme; 2001.

Chapter 6
Pathogens of Aspiration Pneumonia Based on a Novel Approach: Are the Causative Bacteria Different from Those of CAP or HAP?

Toshinori Kawanami and Kazuhiro Yatera

Abstract The causative bacteria of aspiration pneumonia have greatly changed in the last five decades. Anaerobes were believed to be the main causative bacteria of aspiration pneumonia since the 1970s, accounting for 80–90%, and anti-anaerobe agents were recommended for treating aspiration pneumonia. However, the frequency of detection of anaerobes as causative pathogens in patients with aspiration pneumonia has significantly declined since the 2000s. Based on the concept that aspiration pneumonia is generally caused by an invasion of oral bacteria into the lower respiratory tract, it is important to precisely detect and evaluate oral bacteria including anaerobes as causative bacteria in patients with aspiration pneumonia. However, it is usually difficult to evaluate whether oral bacteria are pathogenic or not in the lower respiratory tract infection when culture method using sputum that pass through the oral cavity from the lower respiratory tract is positive for oral bacteria.

Recent development of molecular biological methods, such as targeted polymerase chain reaction, that are independent from culture has made it possible to overcome the above-mentioned difficulties by comprehensively evaluating bacterial flora rather than detecting specific bacterial species. In molecular analysis using 16S ribosomal RNA gene of bronchoalveolar lavage fluid (BALF) in pneumonia patients, assumed causative pathogens of aspiration pneumonia were mainly oral streptococci, and anaerobes were not the main causative bacteria. Even in community-onset pneumonia, oral streptococci were mainly detected in patients with poor functional status. In hospital-acquired pneumonia, *Corynebacterium* spp. were frequently detected from the lower respiratory tract, although oral streptococci were mostly involved. The results of culture-independent molecular methods in BALF may indicate that so-called potentially drug-resistant pathogens such as

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Pseudomonas aeruginosa and methicillin-resistant *Staphylococcus aureus* tend to be overestimated by culture methods, and detecting anaerobes may be strongly influenced by poor oral hygiene status. These changes in bacteriology are thought to occur due to differences in clinical backgrounds, sanitary situation including oral hygiene and care, and analytic methods, and continuous evaluation and monitoring are necessary to elucidate the relationship between detected pathogens and the clinical factors in patients with aspiration pneumonia.

Keywords Aspiration pneumonia · 16S ribosomal RNA gene · Sanger method · Next generation sequencing · Microbiome

1 Introduction

The epidemiology of causative bacteria of aspiration pneumonia has greatly changed in the last four to five decades. In the 1970s and 1980s [1–4], the causative bacteria of aspiration pneumonia were mainly anaerobes, and antibacterial agents covering these bacteria were recommended for the treatment of aspiration pneumonia [5–7]. In the 2000s, the frequency of detecting anaerobes gradually decreased in the studies searching causative bacteria of aspiration pneumonia, and gram-negative bacilli (especially enteral gram-negative bacteria) has been more paid attention [8–11]. In addition to the application of culture-independent molecular methods, different clinical background such as sanitary conditions and oral hygiene, changes in specimens to be examined, and their collecting methods may greatly be related to these changes in causative bacteria of aspiration pneumonia [11, 12].

With the combination of obtaining bronchoalveolar lavage fluid (BALF) samples directly from the lesions of pneumonia, culture methods, and comprehensive and culture-independent molecular methods of bacterial floral analysis using 16S ribosomal RNA (rRNA) gene that enable us to evaluate difficult-to-detect bacteria such as anaerobes, the relationship between oral streptococci and anaerobes and pneumonia has been elucidated in addition to known major causative bacteria [13–15]. These approaches have two advantages over conventional culture methods: comprehensive detection of bacterial species and the ratio of each bacterial species in the sample (bacterial flora). In particular, anaerobes and oral streptococci are both difficult to culture or evaluate properly as causative pathogens of pneumonia, and these approaches are suitable for evaluating the major oral resident bacteria that are closely related to aspiration pneumonia.

This section overviews the transition and its background of the epidemiology of causative bacteria of aspiration pneumonia and new approaches for detecting pathogens focusing on genetic analysis with some precautions.

2 Changes in the Causative Bacteria of Aspiration Pneumonia

2.1 1970s–2000: Evaluation of Bacterial Pathogens by Culture Methods Using Transtracheal Aspirates

Based on the investigation of causative bacteria in hospitalized patients with aspiration pneumonia conducted in the 1970s and 1980s, anaerobes were the most important causative bacteria of aspiration pneumonia. These findings were based on two studies conducted by Bartlett et al. [1, 2] that detected anaerobic bacteria in 50 of 54 (93%) patients with aspiration pneumonia by culture methods using transtracheal aspiration (TTA) specimens [1]. An additional study detected anaerobes in 61 of 70 (87%) patients with aspiration pneumonia in TTA cultures [2]. In these two studies, anaerobes were the main causative agent of aspiration pneumonia, but around 40% of all patients had mixed infections with aerobic and anaerobic bacteria [1, 2]. Other studies in the 1970s [3–6] also showed that anaerobic bacteria were the main causative organisms, and many patients with aspiration pneumonia had pleuritis (pleuropneumonia). Furthermore, multiple anaerobic and aerobic bacteria were detected in patients in whom anaerobes were detected, and the detected species were *Bacteroides* spp., *Fusobacterium* spp., *Peptostreptococcus* spp. (based on the changes in nomenclature of bacterial species by molecular phylogenetic analysis, a part of *Bacteroides* spp. might possibly be *Prevotella* spp. and a part of *Peptostreptococcus* spp. might possibly be *Parvimonas* spp.) [1–6]. Aerobic/facultative bacteria in mixed infections with aerobic and anaerobic bacteria included *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Klebsiella* spp. [1–4]. In addition to anaerobes, causative organisms detected from nosocomial onset aspiration pneumonia patients that showed overt aspiration were similar to those causing nosocomial bacteria such as enteral bacteria and *Pseudomonas aeruginosa* [16, 17]. Sufficient data are still unavailable so far, but anaerobes are more likely to be detected in non-intubated patients with aspiration pneumonia than in intubated patients [6]. Different sampling, detection methods, and clinical and social background of the patients and societies may influence the detection of bacterial species; the detection frequency of anaerobic bacteria as causative pathogens of aspiration pneumonia has drastically been decreasing with time in these five decades.

2.2 Since 2000: Evaluation of Bacterial Pathogens by Culture Method Using Sputum and Lower Respiratory Tract Specimens

Since 2000, *S. pneumoniae*, *Haemophilus influenzae*, and *S. aureus* were mainly detected as causative bacteria of aspiration pneumonia, and the frequency of the detection of anaerobes was significantly decreased than before [7–10]. In the report

Table 6.1 Prevalence of anaerobic cultures in studies involving community-acquired aspiration pneumonia

Authors	Year	Total patients enrolled	Specimens	Procedures	Percentage of patients with anaerobic infection (%)
Bartllet JM, et al. [1]	1974	54	TTA	Culture	92
Lorber B, et al. [3]	1974	47	TTA, TTNA	Culture	62
Bartllet JM, et al. [2]	1975	70	TTA	Culture	87
Cesar L, et al. [4]	1975	17	TTA, TTNA	Culture	100
El-Solh AA, et al. [8]	2003	95	BAL	Culture	14
Tokuyasu H, et al. [9]	2009	62	TTA	Culture	27
Lanspa MJ, et al. [10]	2013	628	TTA	Culture	2

TTA trantracheal aspirate, *TTNA* transthoracic needle aspiration, *BAL* bronchoalveolar lavage fluid

by El-Solh et al. [8], culture results of BALF obtained within 4 h of intratracheal intubation in 95 ventilated patients with severe aspiration pneumonia in the United States showed that 54 (56.8%) patients were positive for at least one bacterial species, and anaerobic bacteria and facultative bacteria (*Enterobacteriaceae* such as *Escherichia coli* and *Klebsiella* spp. and *S. aureus*) were present in 11 (11.6%) and 43 (45.3%) patients, respectively. In a Japanese study, anaerobic bacteria and Gram-negative bacilli were detected in 22 (35.5%) and 32 (51.6%) of 62 Japanese patients with aspiration pneumonia [9]. A large-scale community-acquired pneumonia (CAP) study conducted in the United States showed that anaerobic bacteria were detected in 2% of 628 cases of aspiration pneumonia [10], and anaerobes were detected in 4% of culture-positive patients [18]. Table 6.1 shows the results of a study examining the detection rate of anaerobes over the past several decades. There have been significant changes in causative bacteria in patients with aspiration pneumonia. Until 2000, the main causes of aspiration pneumonia were anaerobes, but the detection rate of anaerobes has significantly declined since 2000, and facultative bacteria, mainly *S. pneumoniae* and intestinal bacteria, have become major causative bacteria (Table 6.1). Aspiration pneumonia occurs in patients with CAP with risk factors for aspiration [19–22], and Hayashi [19] et al. retrospectively compared the clinical background and causative pathogens of 206 patients; they divided patients into two groups: aspiration pneumonia group (n = 96) and non-aspiration pneumonia group (n = 110). Compared with the aspiration pneumonia group, *S. pneumoniae* was frequently detected in the non-aspiration pneumonia group (15.6% vs. 30.6%, p = 0.010), but *E. coli* (10.4% vs. 2.7%, p = 0.024), *Klebsiella* spp. (14.6% vs. 4.5%, p = 0.013) and *S. aureus* (24.0% vs. 10.9%, p = 0.013) were significantly more detected in the aspiration pneumonia group, and the detection of *P. aeruginosa* was not significantly different between these two groups (p = 0.880) [19]. Detection of multidrug-resistant (MDR) pathogens such as methicillin-resistant *S. aureus* (MRSA), MDR *P. aeruginosa*, and extended spectrum beta-lactamase (ESBL)-producing *E. coli* tended to be slightly higher but no statistically significant difference between these two groups (12.5% vs. 7.3%, p = 0.206) [19].

3 Novel Approach for Detecting Causative Bacteria of Pneumonia Independent of Culture

3.1 Benefits and Precautions of the Analysis Using Molecular Biological Methods in Respiratory Diseases

Sputum culture and urinary antigens are often used to detect causative pathogens of pneumonia, but there are several bacteria such as anaerobes and *Legionella* spp. that are sometimes difficult to detect using culture methods. In particular, aspiration pneumonia develops by aspirating indigenous bacteria together with oral secretions and gastroesophageal contents; therefore, it is clinically very important to accurately evaluate whether oral streptococci and anaerobes, which can be causative bacteria of pneumonia, are causative bacteria or not when they are cultured in the respiratory samples. Since around the 1990s, new approaches using molecular biological methods have been introduced complementary to culture methods.

Based on advances in nucleotide sequence analysis technology, these methods comprehensively analyze amplified 16S rRNA genes that are unique to bacteria and archaea by polymerase chain reaction (PCR) using universal primers set in the conserved region, estimating bacterial species by analyzing the base sequence of the variable region of the amplicon. This technique is also useful for estimating bacterial species that are impossible or very difficult to identify with culture methods. Furthermore, clone library analysis has been carried out as bacterial floral analysis using 16S rRNA gene to grasp bacterial flora in the sample by creating a clone library of PCR amplicons of 16S rRNA gene and then evaluating the nucleotide sequence of each clone using Sanger's method. On the other hand, with the advent of the next generation sequencing (NGS) technologies in the 2000s, even though the read lengths are relatively short (100–600 bp), very quick analysis of quite a large number of base sequences such as 1–1000 million reads has been available, and microbiome analysis in the respiratory system has been spurred. NGS demonstrated numerous bacterial floral information in the lower respiratory tract of healthy individuals and non-infectious diseases that were previously believed sterile [23–26]. However, the accuracy of each single sequence read in NGS may be inferior to Sanger's sequencing because NGS guarantees consistency and accuracy by reading a large amount of relatively short and low-quality sequence reads with insufficient length of sequences to detect bacterial DNA at bacterial species level [25, 27]; therefore, attention must be paid when used to identify causative bacterial species in infectious diseases. Since sequencing methods require a certain time for analysis, semi-comprehensive analysis using multiplex PCR has also been carried out to rapidly investigate causative agents of pneumonia [18, 28]. In the report that investigated 2259 cases of CAP using culture method (controlled by quantitative culture) and multiplex PCR in patients with CAP [18], some pathogens including viruses were detected in 853 cases (38%). In addition, using complex molecular testing by multiplex PCR (including culture) detected some pathogens including viruses in 280 (86.7%) among 323 cases of CAP [28]. Although the detection rate of the

pathogen is expected to increase using multiplex PCR for the detection of anticipated pathogens, detection of unexpected pathogens is relatively difficult due to specific detection of certain pathogens. In this chapter, we describe microbiome analysis targeting bacterial 16S rRNA gene.

3.2 Bacteriology of Community-Onset Pneumonia Using Microbiome Analysis

From the viewpoint of selecting antimicrobials for different causative pathogens of pneumonia that depend on the risk factors and ratio of drug-resistant bacteria and mortality, adult pneumonia had historically been categorized into CAP and hospital-acquired pneumonia (HAP), depending on the location of the development of pneumonia. Based on the 2005 American Thoracic Society/Infectious Diseases Society of America guidelines [29], among CAP patients, CAP with risk factors for drug-resistant bacteria [29] was newly classified as healthcare-associated pneumonia (HCAP). However, a subsequent study suggested the skeptical results for the need to categorize CAP and HCAP separately [30], and recently it is more common that "CAP and HCAP" are categorized as "community-onset pneumonia [11]. This section refers to CAP and HCAP separately.

In a Japanese study by Yamasaki et al. [13] that compared the causative bacterial species detected in 64 CAP cases by the clone library analysis and culture methods using BALF samples directly obtained from pneumonia lesions and sputum, culture methods of sputum and BALF samples could not reveal the causative bacteria in 32 cases (50%) and 12 cases (18.8%), respectively, while the clone library analysis of BALF amplified some 16S rRNA gene detected the causative bacterial species in all cases [13]. BALF clone library analysis revealed that known causative bacteria such as *S. pneumoniae* (12/64, 18.8%), *H. influenzae* (12/64, 18.8%), and *Mycoplasma pneumoniae* (11/64, 17.2%) were mainly detected, and anaerobes and oral streptococci were detected as the most predominant phylotypes in 10 patients (15.6%), similar to the report that evaluated causative organisms in severe CAP patients using NGS [31]. Even though this study included a relatively small number of patients and without adjustment of clinical background by age groups, it was surprising that the proportion of anaerobes as the most dominant phylotypes was relatively higher in younger patients, the rates of anaerobes were 25% (3/12) in patients under 40, 23% (3/13) in patients between 40 and 64, and 10% (4/34) in patients aged 65 years or older [13]. In addition to patients with CAP, the same research group showed etiological data of causative pathogens in Japanese patients with HCAP [14] and HAP [15] using the same methods. Table 6.2 shows the results of causative pathogens in these three categories of pneumonia. In the study of 82 Japanese patients with HCAP [14], similar to previous culture methods [11, 16, 17, 21, 32], *S. pneumoniae*, *H. influenzae*, and *H. influenzae*, which are the main causative organisms of CAP, are mostly detected as the dominant bacteria in BALF, and oral streptococci and anaerobes were detected in 19 (23.2%) and 8 patients (9.8%), respectively. Surprisingly, patients with HCAP [14], which may have higher aspiration risks such as poor

Table 6.2 Bacteriology of community-acquired, healthcare-associated, and hospital-acquired pneumonia using clone library analysis of 16S ribosomal RNA gene

Community-acquired pneumonia			Healthcare-associated pneumonia			Hospital-acquired pneumonia		
Yamasaki K, et al. [13]			Noguchi S, et al. [14]			Yatera K, et al. [15]		
Phylotype (n = 64)	n	(%)	Phylotype (n = 82)	n	(%)	Phylotype (n = 68)	n	(%)
Streptococcus pneumoniae	12	(18.8)	Oral streptococci	19	(23.2)	Oral streptococci	11	(16.2)
Haemophilus influenzae	12	(18.8)	*Haemophilus influenzae*	14	(13.1)	*Corynebacterium* spp.	8	(11.8)
Mycoplasma pneumoniae	11	(17.2)	*Streptococcus pneumoniae*	9	(11.0)	Anaerobes	7	(10.3)
Anaerobes	10	(15.6)	*Pseudomonas aeruginosa*	8	(9.8)	*Haemophilus influenzae*	6	(8.8)
Oral streptococci	6	(9.4)	Anaerobes	8	(9.8)	*Neisseria* spp.	6	(8.8)
Moraxella spp.	6	(9.4)	*Staphylococcus aureus*	6	(7.3)	*Enterococcus* spp.	5	(7.4)
Neisseria spp.	3	(4.7)	*Corynebacterium* spp.	4	(4.9)	*Pseudomonas aeruginosa*	5	(7.4)
Staphylococcus aureus	2	(3.1)	*Klebsiella* spp.	3	(3.7)	*Staphylococcus aureus*	4	(5.9)
Corynebacterium spp.	1	(3.1)	*Escherichia coli*	2	(2.4)	*Escherichia coli*	4	(5.9)
Pasteurella spp.	1	(1.6)	*Neisseria* spp.	2	(2.4)	*Staphylococcus epidermidis*	2	(2.9)
						Serratia spp.	2	(2.9)

functional status, showed lower detection rate of anaerobes (9.8%) than CAP (15.6%) [13]. Additive analysis by Akata et al. [33] retrospectively divided the patients into two groups according to the presence or absence of aspiration risks, and oral streptococci were significantly more detected in patients with aspiration risks; in contrast, anaerobes were significantly more detected in patients without aspiration risks. Multivariate analysis for detecting oral streptococci showed that Eastern Cooperative Oncology Group performance status 3 or higher and a history of pneumonia within 1 year were independent risk factors [33]. These results of the molecular method using BALF may indicate that detecting anaerobes in the lung is inversely associated with aspiration or aspiration risks. On the other hand, detection of oral streptococci in the lower respiratory tract is proportional to aspiration or aspiration risks.

3.3 Bacteriology of HAP Using Microbiome Analysis

Using the clone library analysis and culture methods of BALF in 68 Japanese HAP patients [15], culture methods detected some bacteria in 53 (77.9%) patients, and *S. aureus* (30.9%) was most frequently detected, followed by *P. aeruginosa* (16.2%)

and *E. coli* (10.3%), similar to previous reports [16, 17]. The clone library analysis revealed that bacterial rDNA was amplified in 65 (95.6%) patients, and oral streptococci (16.2%), *Corynebacterium* spp. (11.8%), and anaerobes (10.3%) were detected as the most predominant bacterial phylotypes. Unlike the results in patients with CAP [13] and HCAP [14], which showed similar results of main causative bacteria in both culture and the molecular method, the results of the clone library analysis in patients with HAP were greatly different from the results of culture methods. Detection of oral bacteria as top three predominant bacterial species may be supported by a much higher incidence of aspiration pneumonia in HAP patients than in CAP patients [34]. Particularly, even though in patients in whom previously proposed potentially drug-resistant (PDR) pathogens such as *P. aeruginosa*, MRSA, ESBL-producing *Enterobacteriaceae* [29] were detected as predominant species in culture methods, these bacterial species of potentially PDR pathogen were not detectable by the clone library analysis in the lung [13–15].

In relation to the detection of MRSA, Kawanami et al. analyzed bacterial flora of BALF by the clone library analysis in 42 pneumonia patients in whom MRSA was cultured from the lower respiratory tract samples [35]. Among these 42 patients, 28 patients were successfully treated without anti-MRSA agents (assuming non-MRSA pneumonia), and *S. aureus* (corresponding to MRSA) was detected as the most predominant bacterial phylotype in only five (17.9%) patients; particularly, less than 10% occupancy rate of *S. aureus* was found in 19 patients (67.9%) by the clone library analysis. These results may suggest that MRSA may be overestimated as causative pathogens of pneumonia with culture methods, even though MRSA is cultured in sputum or BALF samples [35].

4 Relationship Between Oral Hygiene and Pneumonia

Aspiration consists of four factors: compromised host defense, impaired swallowing function, age-related aspiration, and impaired consciousness [6, 7]; poor oral hygiene as a risk factor for the onset of pneumonia [36] is also a risk factor for aspiration pneumonia [6, 37]. Repetitive aspiration of oral bacteria with saliva with the above factors causes aspiration pneumonia, and evaluation of oral hygiene is necessary and important for a better understanding of aspiration pneumonia. Much attention has currently been paid to the relationship between oral bacterial flora and the development of pneumonia, especially aspiration pneumonia [37–42]. El-Solh et al. [38] evaluated oral and dental hygiene status of 49 pneumonia patients in ICU that developed pneumonia in long-term care facilities and found that 28 (57%) of these patients had dental plaques with cultural detection of *S. aureus*, enteric Gram-negative bacilli, and *P. aeruginosa*, indicating that these dental plaques might possibility be bacterial reservoir for developing pneumonia. In an analysis of the bacterial flora of the tongue of 173 elderly people in the care facility using NGS, participants were divided into two community-types (Type 1; dominated by *Prevotella* spp. and *Veillonella* spp., and Type 2; dominated by *Neisseria* spp. and

Fusobacterium spp.) by principal coordinate analysis. Compared to the adjusted hazard ratio (aHR) of pneumonia-related mortality of 3.79 (confident interval; CI, 1.38–10.39) in Type 1, Type 2 showed higher aHR of 13.88 (CI: 1.64–11.21), suggesting that pneumonia mortality may differ depending on the bacterial floral pattern of the tongue [39].

5 Reasons for Changes in the Causative Bacteria of Aspiration Pneumonia with Time

The reason for the change in causative bacteria of aspiration pneumonia has been unclear so far, and further examinations are necessary to elucidate it. There were several studies that showed frequent detection of anaerobes as pathogens [1–4], but in these studies, (1) there were many cases of lung abscess/necrotizing pneumonia (18.5–70.6%) and empyema with the sample collection period long time after the onset of disease, (2) TTA for sampling itself might possibly cause aspiration and consequent possible overestimation of anaerobic bacteria, (3) some studies included many patients with chronic alcoholic patients and those under general anesthesia as the background diseases [12]. Aspiration pneumonia develops mainly due to oral bacterial aspiration, and comprehensive bacterial floral analysis of the saliva in healthy subjects revealed that *Streptococcus* spp. (54.5%), *Neisseria* spp. (14.7%), *Actinomyces* spp. (8.4%), *Gemella* spp. (4.1%), *Granulicatella* spp. (3.8%), and anaerobes were not detectable in the saliva as the predominant phylotypes [40]. Predominant detection of oral streptococci by the molecular method in the bacterial flora of oral swabs and saliva in stroke patients was reported [41], consistent with the results of the molecular method of the BALF that oral streptococci may be the main causative agent of aspiration pneumonia [33].

In relation to prophylactic effect of oral care for the development of pneumonia, a study with 366 Japanese residents in Japanese in-house care facility showed that residents received professional oral care showed 40% reduction of developing pneumonia compared with those did not receive it [43]. Oral care has strongly been recommended to prevent pneumonia (especially aspiration pneumonia) since several reports have shown the suppressive effect of oral care on the development of pneumonia [37]. In relation to the association of oral hygiene and causative pathogens of pneumonia, poor oral hygiene was related to the detection of anaerobic bacteria in the lower respiratory tract in Japanese pneumonia patients [43]. Oral hygiene assessments using four indices, “oral dryness,” “oral hygiene index (OHI)” as tooth cleaning status index, “tongue coating score” as tongue cleaning status index, and “community periodontal index for treatment needs (CPITN)” as periodontal disease index, were evaluated by specialized dentists, and three indices of oral hygiene status except the tongue coating score were significantly associated with a detection of anaerobes in the lower respiratory tract [43]. Collectively, proper oral care and keeping good oral hygiene status may reduce the incidence of pneumonia including aspiration pneumonia due to a reduction of bacterial burden in the lower respiratory tract.

6 Conclusion

Large scale microbiome analysis has recently become possible and many new findings have emerged that could not be known by culture methods. However, the etiology of causative bacteria of aspiration pneumonia has drastically changed due to clinical backgrounds such as age, lifestyle, dietary differences, functional status, and nutritional status, the clinical background of each subject, specimens and collection methods, and analytic methods; therefore, clinical and methodological background information is very important for precise interpretation. The frequency of detection of anaerobic bacteria as the main causative pathogens of aspiration pneumonia started decreased in the 1970s due to various factors. Considering the mechanism of the pathogenesis of aspiration pneumonia, the results of the BALF analysis using the 16S rRNA gene that oral streptococci were mainly detected as causative pathogens of aspiration pneumonia might be reasonable. Considering the relationship between pneumonia caused by anaerobes and poor oral hygiene, a decrease in anaerobic bacteria as the main pathogens in patients with aspiration pneumonia with time may partly be explained by the progress in oral care.

References

1. Bartlett JM, Gorbach SL, Finegold SM. The bacteriology of aspiration pneumonia. Am J Med. 1974;56:202–7.
2. Bartlett JM, Gorbach SL. The triple threat of aspiration pneumonia. Chest. 1975;68:560–6.
3. Lorber B, Swenson RM. Bacteriology of aspiration pneumonia. A prospective study of community- and hospital-acquired cases. Ann Intern Med. 1974;81:329–31.
4. Cesar L, Gonzalez C, Calia FM. Bacteriologic flora of aspiration-induced pulmonary infections. Arch Intern Med. 1975;135:711–4.
5. DiBardino DM, Wunderink BG. Aspiration pneumonia: a review of modern trends. J Crit Care. 2015;30:40–8.
6. Rodriguez AE, Restrepo MI. New perspectives in aspiration community acquired pneumonia. Expert Rev Clin Pharmacol. 2019;12:991–1002.
7. Mandell LA, Niederman MS. Aspiration pneumonia. N Engl J Med. 2019;380:651–63.
8. El-Sohl AA, Pietrantoni C, Bhat A, Aquilina BA, Okada M, Grover V, et al. Microbiology of severe aspiration pneumonia in institutional elderly. Am J Crit Care Med. 2003;167:1650–4.
9. Tokuyasu H, Harada T, Watanabe E, Okazaki R, Touge H, Kawasaki Y, et al. Effectiveness of meropenem for the aspiration pneumonia in elderly patients. Intern Med. 2009;48:129–35.
10. Lanspa MJ, Jones BE, Brown SM, Dean NC. Mortality and morbidity, and disease severity of patients with aspiration pneumonia. J Hosp Med. 2013;8:83–90.
11. Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American thoracic society and infectious diseases society of America. Am J Respir Crit Care Med. 2019;200:e45–67.
12. Marik PE. Aspiration pneumonitis and aspiration pneumonia. N Engl J Med. 2001;344:665–71.
13. Yamasaki K, Kawanami T, Yatera K, Noguchi S, Fukuda K, Akata K, et al. Significance of anaerobes and oral bacteria in community-acquired pneumonia. PLoS One. 2013;8:e63103.

14. Noguchi S, Mukae H, Kawanami T, Yamasaki K, Fukuda K, Akata K, et al. Bacteriological assessment of healthcare-associated pneumonia using a clone library analysis. PLoS One. 2015;10:e0124697.
15. Yatera K, Noguchi S, Yamasaki K, Kawanami T, Fukuda K, Naito K, et al. Determining the possible etiology of hospital-acquired pneumonia using a clone library analysis in Japan. Tohoku J Exp Med. 2017;242:9–17.
16. Torrs A, Niederman MS, Chastre J, Ewig S, Fernandez-Vandellos P, Hanberger H, et al. International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia. Eur Respir J. 2017;50:1700582.
17. Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney AD, Palmer LB, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the infectious diseases society of America and the American thoracic society. Clin Infect Dis. 2016;63:e61–e111.
18. Jain S, Self WH, Wunderink RG, Fakhran S, Balk R, Bramley AM, et al. Community-acquired pneumonia requiring hospitalization among U.S. adults. N Engl J Med. 2015;373:415–27.
19. Hayashi M, Iwasaki T, Yamazaki Y, Takayasu H, Tateno H, Tazawa S, et al. Clinical features and outcomes of aspiration pneumonia compared with non-aspiration pneumonia: a retrospective cohort study. J Infect Chemother. 2014;20:436–42.
20. Marik PE, Kaplan D. Aspiration pneumonia and dysphagia in the elderly. Chest. 2003;124:328–36.
21. Komiya K, Ishii H, Umeki K, Mizunoe S, Okada F, Johkoh T, et al. Impact of aspiration pneumonia in patients with community-acquired pneumonia and healthcare-associated pneumonia: a multicenter retrospective cohort study. Respirology. 2013;18:514–21.
22. Taylor JK, Flemming GB, Siganayagam A, Hill AT. Risk factors for pneumonia aspiration pneumonia in community-acquired pneumonia: analysis of a hospitalized UK cohort. Am J Med. 2013;126:995–1001.
23. Segal LN, Rom W, Weiden M. Lung microbiome for clinicians: new discoveries about bugs in healthy and diseased lungs. Ann Am Thorac Soc. 2014;11:108–16.
24. Mammen MJ, Sethi S. COPD and the microbiome. Respirology. 2016;21:590–9.
25. Yatera K, Noguchi S, Mukae H. The microbiome in the lower respiratory tract. Respir Investig. 2018;56:432–9.
26. Salisbury ML, Han MK, Dickson RP, Molyneaux PL. Microbiome in interstitial lung disease: from pathogenesis to treatment target. Curr Opin Pulm Med. 2017;23:404–10.
27. Fukuda K, Ogawa T, Taniguchi H, Saito M. Molecular approaches to studying microbial communities: targeting the 16S ribosomal RNA gene. J UOEH. 2016;38:223–32.
28. Gadsby NJ, Russell CD, McHugh MP, Mark H, Conway Morris A, Laurenson FI, et al. Comprehensive molecular testing for respiratory pathogens in community-acquired pneumonia. Clin Infect Dis. 2016;62:817–23.
29. American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA). Guidelines for the management of adults with hospital-acquired pneumonia, ventilator-associated pneumonia, and healthcare-associated pneumonia. Am J Respir Crit Care Med. 2005;171:388–416.
30. Ewing S, Welte T, Chastre J, Torres A. Rethinking the concepts of community-acquired pneumonia and healthcare-associated pneumonia. Lancet Infect Dis. 2010;10:274–87.
31. Bousbia S, Papazian L, Saux P, Forel JM, Auffray JP, Martin C, et al. Repertoire of intensive care unit pneumonia microbiota. PLoS One. 2012;7:e32486.
32. Ishida T, Tachibana H, Ito A, Yoshioka H, Arita M, Hashimoto T. Clinical characteristics of nursing and healthcare-associated pneumonia: a Japanese variant of healthcare-associated pneumonia. Intern Med. 2012;51:2537–44.
33. Akata K, Yatera K, Yamasaki K, Kawanami T, Naito K, Noguchi S, The significance of oral streptococci in patients with pneumonia with risk factors for aspiration, et al. The bacterial flora analysis of 16S ribosomal RNA gene using bronchoalveolar lavage fluid. BMC Pulm Med. 2016;16:79.

34. Teramoto S, Fukuchi Y, Sasaki H, Sato K, Sekizawa K, Matsuse T, et al. High incidence of aspiration pneumonia in community- and hospital-acquired pneumonia in hospitalized patients: a multicenter, prospective study in Japan. J Am Geriatr Soc. 2008;56:577–9.
35. Kawanami T, Yatera K, Yamasaki K, Fukuda K, Noguchi S, Akata K, et al. Clinical impact of methicillin-resistant *Staphylococcus aureus* on bacterial pneumonia: cultivation and 16S ribosomal RNA gene analysis of bronchoalveolar lavage fluid. BMC Infect Dis. 2016;16:155.
36. Abe S, Ishihara K, Adachi M, Okuda K. Tongue-coating as risk indicator for aspiration pneumonia in edentate elderly. Arch Gerontol Geriatr. 2008;47:267–75.
37. Pace CC, McCullough GH. The association between oral microorgansims and aspiration pneumonia in the institutionalized elderly: review and recommendations. Dysphagia. 2010;25:307–22.
38. El-Solh AA, Pietrantoni C, Bhat A, Okada M, Zambon J, Aquilina A, et al. Colonization of dental plaques: a reservoir of respiratory pathogens for hospital-acquired pneumonia in institutionalized elders. Chest. 2004;126:1575–82.
39. Kageyama S, Takeshita T, Furuta M, Tomioka M, Asakawa M, Suma S, et al. Relationship of variations in the tongue microbiota and pneumonia morality in nursing residents. J Gerontol A Biol Sci Med Sci. 2018;73:1097–102.
40. Akiyama T, Miyamoto H, Fukuda K, Sano N, Katagiri N, Shobuike T, et al. Development of a novel PCR method to comprehensively analyze salivary bacterial flora and its application to patients with odontogenic infections. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2010;109:669–76.
41. Boaden E, Lyons M, Singhrao SK, Dickinson H, Leathley M, Lightbody C, et al. Oral flora in acute stroke patients: a prospective exploratory observational study. Gerondontology. 2017;34:343–56.
42. Yoneyama T, Yoshida M, Ohrui T, Mukaiyama H, Okamoto H, Hoshiba K, et al. Oral care reduces pneumonia in older patients in nursing homes. J Am Geriatr Soc. 2002;50:430–3.
43. Hata R, Noguchi S, Kawanami T, Yamasaki K, Akata K, Ikegami H, et al. Poor oral hygiene is associated with the detection of obligate anaerobes in pneumonia. J Periodontol. 2020;91(1):65–73.

Chapter 7
Antimicrobial Selection for Aspiration Pneumonia: What Is the Important Point of Antimicrobial Selection for Aspiration Pneumonia?

Tadashi Ishida

Abstract Aspiration pneumonia is pneumonia resulting from abnormal entry of food or oral content into the lower airway. Oral streptococci and anaerobes are therefore thought to play an important role in its etiology. Moreover, the common pathogens detected in pneumonia patients without aspiration are also isolated from patients with aspiration pneumonia.

Selection of antimicrobials for use in aspiration pneumonia is standardized by the Japanese Respiratory Society guidelines for nursing and healthcare-associated pneumonia, taking severity, sepsis, and risk of drug-resistant pathogens into consideration. Escalation or de-escalation tactics are decided taking into account the clinical history of the patient. A regimen with activity against both aerobes and anaerobes should be selected as an empirical therapy. In general, penicillin combined with a β-lactamase inhibitor is recommended as the first-line antimicrobial. Patients who are initially treated with parenteral antimicrobials can be switched to oral ones once they show clinical improvement.

Keywords Anaerobes · Nursing and healthcare-associated pneumonia · Guidelines · Drug-resistant pathogens · Penicillin combined with a β-lactamase inhibitor

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1 Introduction

Aspiration pneumonia is pneumonia resulting from abnormal entry of food or contents of the oral cavity into the lower airway. Aspiration may occur even in healthy individuals and usually resolves without sequelae. Those with swallowing dysfunction or an altered clearance defense mechanism can develop pneumonia following the aspiration of microorganisms from the oral cavity or nasopharynx. Most pneumonia cases among the elderly are regarded as aspiration-related [1], and aspiration is an important factor in all types of pneumonia in the elderly. Particularly, aspiration pneumonia is thought to be the main constituent of healthcare-associated pneumonia (HCAP)/nursing and healthcare-associated pneumonia (NHCAP) [2, 3]. It has also been reported that aspiration pneumonia is a significant predictor of mortality among community-acquired pneumonia (CAP) and HCAP patients [4].

Predisposing conditions of aspiration include cerebrovascular disorders, neurologic disorders such as Parkinson's disease or pseudobulbar palsy, drug overuse, poor oral hygiene, alcoholism, general anesthesia, oropharyngeal obstruction, nasogastric tubes, and others. The elderly may have multiple factors combined.

The term aspiration pneumonia includes a chemical pneumonitis resulting from the aspiration of toxic substances such as gastric acid. However, this chapter will refer to the treatment of pneumonia caused by bacterial infection only.

2 Microbiology of Aspiration Pneumonia

The most common forms of aspiration pneumonia are caused by bacteria that colonize the oral cavity, upper airway, or stomach. Thus, aspiration pneumonia has been related to infections caused by oral streptococci or anaerobes. Especially, anaerobes have been thought to play an important role in aspiration pneumonia [5]. However, Marik et al. analyzed the cultures of protected brush specimens or bronchoalveolar lavage specimens from patients with suspected ventilator-associated pneumonia (VAP) and aspiration pneumonia and isolated only one anaerobic organism [6].

Table 7.1 lists the causative pathogens of aspiration pneumonia from three references. El-Solh et al. prospectively investigated the microbial etiology of institutionalized elderly patients with severe aspiration pneumonia [7]. Gram-negative enteric bacilli were the predominant organisms isolated, followed by anaerobic bacteria and *Staphylococcus aureus*. Polymicrobial infection was observed in 22.2% of the patients tested.

The authors analyzed a prospectively collected database of patients with NHCAP and CAP who were hospitalized and the etiology of patients with probable aspiration [8]. The most common pathogen was *Streptococcus pneumoniae*; however, methicillin-resistant *S. aureus* (MRSA) and *Escherichia coli* were detected significantly more often in patients with probable aspiration than in those without probable aspiration. However, this study had a limitation that the incidence of anaerobes

Table 7.1 The microbiology of aspiration-related pneumonia

Microorganism	El-Solh et al. (%)	Ishida et al. (%)	Akata et al. (%)
Streptococcus pneumoniae	9.3	26.0	11.9
Oral streptococci	11.1	11.0	31.0
Staphylococcus aureus (MSSA)	11.1	10.0	4.8
Staphylococcus aureus (MRSA)	3.7	13.0	
Moraxella catarrhalis	–	8.0	6.0
Haemophilus influenzae	3.7	7.0	16.7
Klebsiella spp.	18.5	14.0	3.6
Escherichia coli	24.1	11.0	2.4
Pseudomonas aeruginosa	3.7	12.0	2.4
Anaerobes	20.4	2.0	6.0
Chlamydophila pneumoniae	–	6.0	–
Polymicrobial	22.2	20.0	–

was underestimated due to the fact that bacteriological examination was mainly done by sputum culture.

On the other hand, Akata et al. collected bronchoalveolar fluid (BALF) samples from the affected lesions of pneumonia via bronchoscopy and evaluated them by the bacterial floral analysis of the 16S rebosomal ribonucleic acid (rRNA) gene in addition to the cultivation methods in pneumonia patients with aspiration risk [9]. The dominant pathogens were oral streptococci detected by bacterial floral analysis of the 16S rRNA gene. Interestingly, no methicillin-resistant *Staphylococcus aureus* (MRSA) was detected by gene analysis, although MRSA was cultured in 6% of the BALF samples.

These differences in the etiology are explained by variations in setting (community-acquired, nursing home-acquired, or hospital-acquired), sampling methods (expectorated sputa, blood, protected brush specimen, or bronchoalveolar lavage fluid), or prior use of antimicrobials.

3 Antimicrobial Treatment

3.1 Choice of Antimicrobials

Empirical anaerobic cover for patients with suspected aspiration pneumonia is controversial. The American Thoracic Society and the Infectious Diseases Society of America guidelines for CAP in 2019 advise against the routine addition of anaerobic coverage for suspected aspiration pneumonia unless a lung abscess or empyema is suspected [10]. This is due to the fact that several studies of acute aspiration events [2, 7, 11] have suggested that anaerobes do not play a major role in the etiology, and the use of clindamycin or β-lactam with a β-lactamase inhibitor might increase *Clostridioides difficile* infections.

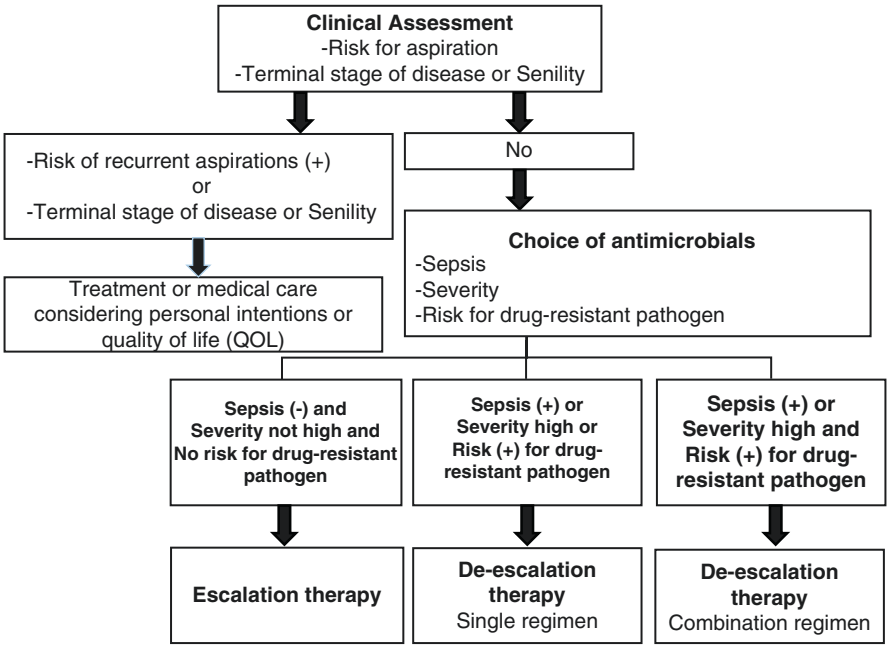

Fig. 7.1 Flowchart for empiric therapy of nursing and healthcare-associated pneumonia (revised from the JRS guidelines)

However, oral bacterial flora that includes anaerobes is thought to play an important role from the study analysis of the flora of alveolar lesions using a genetic method [9]. On the other hand, the common pathogens detected in patients with CAP or HCAP/NHCAP without aspiration are also isolated from patients with aspiration pneumonia. Anaerobic coverage beyond the standard empiric treatment is recommended when microbiological results of various tests have not yet been obtained. A regimen with activity against both aerobes and anaerobes is recommended as an empirical therapy.

As described above, the main constituent of HCAP/NHCAP is thought to be aspiration pneumonia. Thus, recommendations of antimicrobials are indicated in conformity according to the Japanese Respiratory Society (JRS) guidelines for NHCAP [2, 12].

The flowchart of empirical treatment for NHCAP in the guidelines is shown in Fig. 7.1. First, the attending physician needs to evaluate patient background by assessing for aspiration risk factors as well as whether or not they are in the terminal phase of their illness or senile. When recurrent aspirations cannot be avoided due to extinct swallowing function, or they are judged as being in the terminal stage of their illness or having advanced senility, the attending physicians will need to make the decision of treatment or medical care, taking into account the patient's wishes and quality of life.

Table 7.2 qSOFA score

Sepsis is likely if ≥ 2 of the following criteria are met:
Respiratory rate ≥ 22 breaths per min
Altered mentation (Glasgow coma scale < 15)
Systolic blood pressure ≤ 100 mmHg

If the patient does not meet any of the above criteria, antimicrobial therapy is evaluated. Treatment regimens will be selected considering the presence or absence of sepsis, severity of pneumonia, and risk for drug-resistant pathogens. The severity is scored by the A-DROP (Age, Dehydration, Respiration, Orientation, and blood Pressure) system provided in the guidelines of the JRS [12]. The diagnosis of sepsis is made according to the Sequential Organ Failure Assessment (SOFA) score or the qSOFA score [13]. Though we reported that the prognostic performance of qSOFA for in-hospital mortality and intensive care unit (ICU) admission was not significantly different from those of CURB-65 and pneumonia severity index (PSI) [14], it may be useful as a bedside prompt because only a few items or vital signs are required (Table 7.2). Patients are considered to be at risk of drug-resistant pathogens when they fulfill two or more of the following criteria: (a) prior use of antimicrobials within the past 90 days, (b) 2 or more days of hospital admission history within the past 90 days, (c) immunosuppression, or (d) decreased activity (performance status 3 or 4, Barthel index <50, inability to walk, or tube-feeding/total parenteral nutrition).

When the patient is not labeled severe and does not have sepsis or is not at risk of drug-resistant pathogens, escalation therapy should be applied. In this group, target organisms are *S. pneumoniae*, methicillin-sensitive *S. aureus*, *H. influenzae*, oral *Streptococcus* spp., *Klebsiella* spp., and *Moraxella catarrhalis*. Initial treatment should start with a single antimicrobial drug. If the initial therapy is ineffective, or if the isolated organisms are not sensitive to the antimicrobial administered, they should be escalated to other antimicrobials with a broader antibacterial spectrum.

When the patient is assessed as severe, has sepsis, or has a risk factor for drug-resistant pathogens, de-escalation therapy with a single regimen will apply. Target organisms in this and the next group include *Pseudomonas aeruginosa*, extended-spectrum β-lactamase producing Enterobacteriaceae, and MRSA, in addition to the pathogens listed in the previous group. An antimicrobial drug with a broad antibacterial spectrum covering drug-resistant pathogens such as *P. aeruginosa* should be used as an initial therapy. When a causative organism is confirmed, the initial drug should be altered to one with a narrower antibacterial spectrum.

When the patient is assessed as severe, has sepsis, or has a risk factor for drug-resistant pathogens, de-escalation therapy with a combination regimen should be chosen. Two drugs are selected among piperacillin/tazobactam, carbapenems, the fourth-generation cephalosporins, new quinolones, and aminoglycosides. The combination of two β-lactam antibiotics should be avoided. If MRSA infection is suspected, anti-MRSA drugs should be added. Similar to de-escalation therapy with a single regimen, the initial combination should likewise be altered to a narrower antibacterial spectrum or a single regimen.

Table 7.3 Empiric antimicrobial selection for aspiration pneumonia

Severity		Antimicrobials
Mild	The first choice	Clavulanate/amoxicillin with or without amoxicillin
		Sultamicillin
	The second choice	Moxifloxacin Garenoxacin Sitafloxacin Lascufloxacin
Moderate	The first choice	Sulbactam/ampicillin
	The second choice	Ceftriaxone or cefotaxime or levofloxacin with clindamycin or metronidazole
Severe	The first choice	Tazobactam/piperacillin
		Meropenem Doripenem Biapenem Imipenem/cilastatin
	The second choice	Cefozopran or cefepime or cefpirome or levoflovxacin with clindamycin or metronidazole
	MRSA infection is suspected	Plus linezolid or vancomycin or teicoplanin

Careful attention should be paid to the evaluation of isolated organisms via sputum culture. In those with chronic pulmonary disease or those receiving recurrent antimicrobial therapy, drug-resistant pathogens such as *P. aeruginosa* and MRSA often colonize the respiratory tract [15]. Even though these organisms are cultured from their sputum, they may not be causative. It was reported that most NHCAP patients recovered with the use of antimicrobials that did not cover drug-resistant pathogens, even if *P. aeruginosa* or MRSA was isolated from their sputum [16]. In the above-referenced report by Akata et al., *P. aeruginosa* and MRSA are much less frequently isolated by the analysis of the 16S rRNA gene using BALF rather than by sputum culture [9].

With reference to the guidelines described above, the choice of antimicrobials for empirical therapy of patients with aspiration pneumonia is guided by its severity (Table 7.3).

3.1.1 Mild Cases

This group consists of those who are not severely ill and can tolerate an oral regimen in an outpatient setting. Penicillin combined with a β-lactamase inhibitor such as clavulanate/amoxicillin (CVA/AMPC) or sultamicillin (SBTPC) is recommended, considering anaerobe coverage. Use of a high dose of penicillin is desirable. A dose of 1500–2000 mg a day of amoxicillin (AMPC) is recommended for those with normal renal function. AMPC may be added to CVA/AMPC to increase the penicillin dosage. Fluoroquinolones are an alternative for outpatients. Moxifloxacin (MFLX), garenoxacin (GRNX), sitafloxacin (STFX), or a next-generation

quinolone; lascufloxacin are candidates. Levofloxacin (LVFX) is not recommended as it is less effective against anaerobes.

3.1.2 Moderate Cases

This group includes those who require hospitalization, but are not septic and have no risk factors for drug-resistant pathogens. Parenteral therapy is required, and sulbactam/ampicillin (SBT/ABPC) is suggested as the first-line treatment [17]. It has been reported that a penicillin (AMPC) injection with sulbactam (SBT) was as effective and well-tolerated as clindamycin with or without cephalosporin in the treatment of aspiration pneumonia and lung abscesses [18]. The dosage of ABPC-SBT is 1.5–3 g every 6 h for those with normal renal function.

The JRS guidelines recommend ceftriaxone, cefotaxime, or levofloxacin for hospitalized NHCAP patients with moderate severity and no risk for drug-resistant pathogens. However, these drugs are less effective against anaerobes. Thus, they are best avoided, or combined with either clindamycin or metronidazole when aspiration pneumonia is suspected.

If the initial therapy is ineffective or if the specimen culture detects bacteria not sensitive to SBT/ABPC, escalation to another drug with a broader bacterial spectrum might be needed.

3.1.3 Severe Cases

The JRS guidelines divide severe NHCAP into two groups according to two factors: sepsis and the risk for drug-resistant pathogens.

For those who have either sepsis or risk factors, single regimens are recommended. They include tazobactam/piperacillin (TAZ/PIPC), carbapenems, the fourth-generation cephalosporins, or new quinolones. TAZ/PIPC was found to be as effective and safe as imipenem/cilastatin (IPM/CS) in the treatment of moderate-severe aspiration pneumonia [19]. Cephalosporins and the new quinolones should be avoided or used together with clindamycin or metronidazole when aspiration pneumonia is suspected due to their low efficacy against anaerobes.

For patients with both sepsis and risk factors, double regimens are recommended. Two of the following drugs or family of drugs should be selected: PIPC/TAZ, carbapenems, the fourth-generation cephalosporins (cefozopran, cefepime, or cefpirome), the new quinolones, or aminoglycosides. The combination of two β-lactams should be avoided. Cephalosporins, the new quinolones, or aminoglycosides should be avoided or used together with clindamycin or metronidazole when aspiration pneumonia is suspected. Aminoglycosides should also be avoided for those who have poor renal function. And are therefore not recommended for the elderly with aspiration pneumonia.

When MRSA infection is suspected, anti-MRSA drugs such as linezolid, vancomycin or teicoplanin are added. If the patient has a history of MRSA isolation or

intravenous antibiotic therapy in the preceding 90 days, he or she is suspected of having MRSA infection. However, the frequency of aspiration pneumonia due to MRSA is thought to be low as described above; therefore, administration of anti-MRSA drugs should be done with discretion. After having given anti-MRSA drugs, they may be ceased if MRSA is not isolated from their sputa with sufficient quality, or phagocytosis of MRSA is not recognized in the Gram's stain [20].

3.2 Switch to Oral Antimicrobials

Patients who are initially treated with parenteral antimicrobials can be switched to oral ones if they show signs for clinical improvement, have normal gastrointestinal function, and are able to take oral medications. The selection of oral drugs is the same as those for mild cases. In practice, CVA/AMPC is most often administered.

3.3 Duration of Treatment

The duration of antimicrobials for aspiration pneumonia is arbitrary. A systematic review concluded that a short fixed-course (7 or 8 days) of antibiotic therapy may be more appropriate than a prolonged course (10–15 days) for patients with VAP not due to non-fermenting Gram-negative bacilli (NF-GNB) [21]. The usual duration of therapy for patients who are not complicated by lung abscess or empyema is thought to be 7 days. When suppurative lesions exist, treatment for more than 2 weeks is required.

4 Conclusion

Antimicrobials for aspiration pneumonia should be selected taking severity, presence or absence of sepsis, and risk of drug-resistant pathogens into consideration. A regimen with activity against both aerobes and anaerobes is recommended as an empirical therapy.

References

1. Teramoto S, Fukuchi Y, Sasaki H, Sato K, Sekizawa K, Matsuse T. High incidence of aspiration pneumonia in community- and hospital-acquired pneumonia in hospitalized patients: a multicenter, prospective study in Japan. J Am Geriatr Soc. 2008;56(3):577–l.
2. The Japanese Respiratory Society. The JRS guidelines for the management of nursing and healthcare-associated pneumonia in adults. The Japanese Respiratory Society, 2011.
3. Teramoto S, Kawashima M, Komiya K, Shoji S. Health-care-associated pneumonia is primarily due to aspiration pneumonia. Chest. 2009;136:1702–3.

4. Komiya K, Ishii H, Umeki K, Mizunoe S, Okada F, Johkoh T. Impact of aspiration pneumonia in patients with community-acquired pneumonia and healthcare-associated pneumonia: a multicenter retrospective cohort study. Respirology. 2013;18:514–21.
5. Bartlett JG. How important are anaerobic bacteria in aspiration pneumonia. Infect Dis Clin N Am. 2013;27:149–55.
6. Marik PE, Careau MT. The role of anaerobes in patients with ventilator-associated pneumonia and aspiration pneumonia: a prospective study. Chest. 1999;115:178–83.
7. El-Solh AA, Pietrantoni C, Bhat A, Aquilina AT, Okada M, Grover V, et al. Microbiology of severe aspiration pneumonia in institutionalized elderly. Am J Respir Crit Care Med. 2003;167:1650–4.
8. Ishida T, Tachibana H, Ito A, Yoshioka H, Arita M, Hashimoto T. Clinical characteristics of nursing and healthcare-associated pneumonia: a Japanese variant of healthcare-associated pneumonia. Intern Med. 2012;51:2537–44.
9. Akata K, Yatera K, Yamasaki K, Kawanami T, Naito K, Noguchi S, et al. The significance of oral streptococci in patients with pneumonia with risk factors for aspiration: the bacterial floral analysis of 16S ribosomal RNA gene using bronchoalveolar lavage fluid. BMC Pulm Med. 2016;16:79. https://doi.org/10.1186/s12890-016-0235-z.
10. Metlay JP, Waterer GW, Long AC, Anzueto LA, Brozek J, Crothers K, et al. Diagnosis and treatment of adults with community-acquired pneumonia: an official clinical guidelines of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med. 2019;200:e45–63.
11. Mier L, Dreyfuss D, Darchy B, Lanore JJ, Djedaïni K, Weber P, et al. Is penicillin G an adequate initial treatment for aspiration pneumonia? A prospective evaluation using a protected specimen brush and quantitative cultures. Intensive Care Med. 1993;19:279–84.
12. The Japanese Respiratory Society. The JRS guidelines for the management of pneumonia in adults. The Japanese Respiratory Society, 2017.
13. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016;315:801–10.
14. Tokioka F, Okamoto H, Yamazaki A, Itou A, Ishida T. The prognostic performance of qSOFA for community-acquired pneumonia. J Intensive Care. 2018;6:46. https://doi.org/10.1186/s40560-018-0307-7.
15. Angrill J, Agustí C, De Celis R, Filella X, Rañó A, Elena M, et al. Bronchial inflammation and colonization in patients with clinically stable bronchiectasis. Am J Respir Crit Care Med. 2001;164:1628–32.
16. Fukuyama H, Yamashiro S, Tamaki H, Kishaba T. A prospective comparison of nursing- and healthcare-associated pneumonia (NHCAP) with community-acquired pneumonia (CAP). J Infect Chemother. 2013;19:719–26.
17. Teramoto S, Yoshida K, Hizawa N. Update on the pathogenesis and management of pneumonia in the elderly-roles of aspiration pneumonia. Respir Investig. 2015;53:178–84.
18. Allewelt M, Schüler P, Bölcskei PL, Mauch H, Lode H. Ampicillin + sulbactam vs clindamycin +/− cephalosporin for the treatment of aspiration pneumonia and primary lung abscess. Clin Microbiol Infect. 2004;10:163–70.
19. Ito I, Kadowaki S, Tanabe N, Haruna A, Kase M, Yasutomo Y, et al. Tazobactam/piperacillin for moderate-to-severe pneumonia in patients with risk for aspiration: comparison with imipenem/cilastatin. Pulm Pharmacol Ther. 2010;23:403–10.
20. The Japanese Society of Chemotherapy/The Japanese Association for Infectious Diseases. Practical guidelines for the management and treatment of infections caused by MRSA: 2019 edition. http://www.kansensho.or.jp/uploads/files/guidelines/guideline_mrsa_2019revised-booklet.pdf. Accessed 14 June 2019.
21. Pugh R, Grant C, Cooke RP, Dempsey G. Short-course versus prolonged-course antibiotic therapy for hospital-acquired pneumonia in critically ill adults. Cochrane Database Syst Rev. 2015;8:XCD007577.

Part II
Pathophysiology of Aspiration Pneumonia

Chapter 8
The Relationship Between the Risk of Aspiration Pneumonia and the Risk of Aspiration: Aspiration Risk and Aspiration Pneumonia Risk Are Not the Same?

Kosaku Komiya and Jun-Ichi Kadota

Abstract Reported risks for aspiration include cerebrovascular disease, laryngopharyngeal dysfunction, advanced age, severe dementia, Parkinson's disease, malnutrition, the use of antipsychotic drugs, and gastroesophageal reflux. Although the aspiration risks may be included among the risks for aspiration pneumonia, the two sets of risks are not identical, and people with aspiration risk factors do not necessarily develop aspiration pneumonia. The risks for aspiration pneumonia also include factors related to the pathogens and to the host defense. Factors associated with the risk of pathogen infection include oral health, such as bacterial colonization and tooth decay, and the use of proton pump inhibitors, and host defense factors associated with the pathogenesis include advanced age, male gender, a preexisting respiratory disease, angiotensin-converting enzyme genotype, malnutrition, diabetes mellitus, and the use of immunosuppressants. Consideration of the relationships between the pathogen, host, and environment is needed for a better understanding of the mechanisms that underlie aspiration pneumonia and for developing effective strategies for its prevention.

Keywords Aspiration risk · Aspiration pneumonia risk · Host · Pathogen · Environment

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1 Introduction

The terms “aspiration risk” and “aspiration pneumonia risk” are often used interchangeably. However, people with aspiration risk factors do not necessarily develop aspiration pneumonia because other factors are associated with the pathogenesis of the condition. Current Japanese Respiratory Society guidelines for the management of pneumonia in adults describe aspiration risk and aspiration pneumonia risk separately [1]. This chapter focuses on the differences and similarities between the risk of aspiration and the risk of aspiration pneumonia, and discusses the relationships between the pathogen, host, and environment in the development of aspiration pneumonia.

2 Mechanisms Underlying the Development of Aspiration Pneumonia

The definition of aspiration pneumonia is vague, and so this condition cannot be considered a distinct type of pneumonia. Aspiration pneumonia is widely regarded to be pneumonia that occurs in patients with dysphagia [2, 3]; however, dysphagia includes various levels of swallowing dysfunction, and patients with the same level of dysphagia do not necessarily have the same risk for aspiration pneumonia. The development of aspiration pneumonia requires the aspiration and subsequent growth of pathogens such as causative bacteria for pneumonia that have colonized the oral cavity and laryngopharynx [4].

When considering the etiology of infectious diseases, the relationships between the pathogen, the host, and the environment need to be considered [5]. Aspiration risk is an environmental factor. People with the aspiration risk factors are at risk for aspiration pneumonia, and having greater numbers and greater severity of these risk factors is significantly associated with an increased risk for aspiration pneumonia. However, aspirated materials do not always cause aspiration pneumonia. For example, the aspiration of sterile materials would not induce pneumonia. Factors related to the pathogen itself need to be considered, such as its virulence and quantity. Host factors also play a prominent role in the development of aspiration pneumonia. When a person can successfully remove the aspirated pathogens by coughing, he or she can avoid the development of pneumonia. Radiological evidence for the preventive impact of host factors on aspiration pneumonia has been provided by a case study of a patient with normal cough function who had aspirated a large amount of oral secretions after neck surgery; he successfully cleared these aspirated materials, with no signs of pneumonia [6]. Although aspiration risks are regarded as the main factors contributing to the mechanism underlying the development of aspiration pneumonia, these other pathogen, host, and environmental factors should also be considered, as with other infectious diseases.

Table 8.1 Clinical factors reported to be associated with aspiration risk

Category	Factors
Risk factors that specifically reduce swallowing function	Cerebrovascular diseases
	Pharyngolaryngeal surgery
Risk factors that indirectly reduce swallowing function	Advanced age
	Severe dementia
	Parkinson's disease
	Malnutrition
	Use of antipsychotic drugs
Other risk factors	Gastroesophageal reflux

3 Aspiration Risk

Many studies have reported risk factors associated with aspiration pneumonia [7–9]. However, no studies have evaluated how aspiration pneumonia risk differs from aspiration risk or considered the risks separately in terms of pathogen, host, and environmental factors. For example, a systematic review of risk factors related to aspiration pneumonia in older frail people by van der Maarel-Wierink et al. did not discriminate aspiration risk from host or pathogen factors [7].

Table 8.1 summarizes reported risk factors for aspiration, extracted from published studies about aspiration pneumonia risk. These can be classified into three categories based on the underlying mechanisms. The first category comprises the risk factors specifically associated with a decrease in swallowing function, such as cerebrovascular diseases and laryngopharyngeal diseases, including malignancies [10–12]. Cerebrovascular diseases, especially those affecting the deep brain, can specifically affect swallowing function. However, there are inconsistencies in reports of the association between cerebrovascular diseases and aspiration pneumonia in frail older people, although deep cerebral infarcts seem to be more closely associated with the incidence of pneumonia than are superficial infarcts [13, 14]. The second category includes risk factors that are indirectly associated with dysphagia, such as a decreased level of consciousness, severe dementia, Parkinson's disease, and the use of antipsychotic drugs [15]. Advanced age and malnutrition can reduce the strength of muscles related to swallowing, thereby contributing to aspiration risk. The third category includes gastroesophageal reflux, which can be a risk factor for aspiration through interfering with the laryngopharyngeal phase of swallowing [16, 17]. Gastroesophageal reflux is a trigger of silent aspiration, which can also cause diffuse aspiration bronchiolitis [18]. The systematic review by van der Maarel-Wierink et al., cited earlier, reported the following evidence-level categories for the risk factors: advanced age, 2a; severe dementia, 2a; Parkinson's disease, 2b; and the use of antipsychotic drugs or proton pump inhibitors, 3b [7]. However, the definition of each aspiration risk was not unified across the studies included in that review, so these evidence levels may not be definitive.

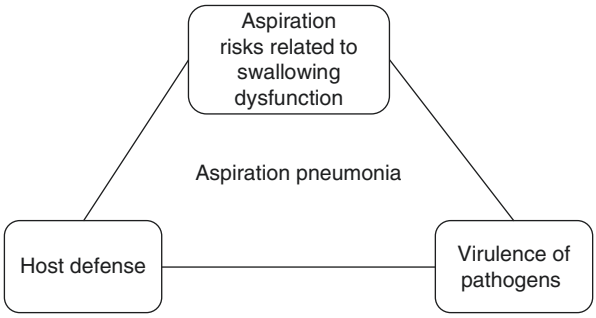

Fig. 8.1 Factors associated with aspiration pneumonia

Table 8.2 Physiological factors associated with aspiration risk

Phase of swallowing	Useful parameter
Oral phase	Respiratory rate
Oral and pharyngeal phases	Tongue strength
Pharyngeal phase	Hyoid movement
	Bolus dwell time in the pharynx while the larynx remains open

Several studies have analyzed dysphagia as a risk factor for aspiration [3, 7, 19]. However, dysphagia results from various conditions associated with decreased swallowing function and so can be a confounder of these variables (Fig. 8.1). Dysphagia is not clearly defined. Swallowing comprises a voluntary oral/preparatory phase, a voluntary oral phase, and involuntary pharyngeal and esophageal phases [20], and difficulties in any of these phases may result in swallowing dysfunction. This makes the definition of dysphagia complicated.

Steele and Cichero systematically reviewed physiological factors associated with aspiration risk [21]. Their review, which included 37 articles, reported that tongue strength, anatomically normalized hyoid movement, respiratory measures, and the length of time the bolus remains in the pharynx with the airway open all had the potential to increase the risk of penetration or aspiration (Table 8.2). However, the authors noted the poor methodological quality of many of the included studies. Only a few of the studies confirmed aspiration status using videofluoroscopy or fiberoptic endoscopy, so the results reported by the review cannot be interpreted as indicative of causative relationships.

4 Risk Factors Associated with the Pathogens

No published studies have focused on the direct association between poor oral health and the incidence of aspiration pneumonia. However, oral healthcare intervention studies have reported that the interventions reduced the risk of developing aspiration pneumonia, and even the risk of death due to aspiration pneumonia, in care-home residents [22, 23]. These results indicate that poor oral hygiene can contribute to the development of aspiration pneumonia.

Sumi et al. investigated oral biofilms in 138 frail older people [4]. In 89 (64.5%) of the cases, potential respiratory pathogens were found to have colonized the oral cavity. The main pathogens isolated were *Staphylococcus aureus* (24.5%), *Klebsiella pneumoniae* (18.1%), *Pseudomonas aeruginosa* (18.1%), and *Enterobacter cloacae* (11.6%). Poor oral health that allows the growth of bacteria and the development of biofilms in mouth may increase the likelihood that aspiration pneumonia develops when oral secretions are aspirated.

There have been studies of the association between dental decay and aspiration pneumonia [24, 25]. The number of decayed teeth and the number of functional dental units have been reported to be associated with aspiration pneumonia [24]. The presence of 10 or more teeth with a probing depth that exceeds 4 mm (the periodontal pocket) has been reported to be a risk factor for death from pneumonia [26]. Conversely, a case–control study that identified risk factors for community-acquired pneumonia found that visiting a dentist during the past month was an independent factor associated with the prevention of pneumonia [27]. Tooth decay may be associated with the growth of anaerobic bacteria [28–30]. The impact of anaerobic bacteria on aspiration pneumonia is uncertain, and whether all patients with aspiration pneumonia should be treated with antibiotics that cover anaerobic bacteria remains under debate [31–33]. If there is clear confirmation of an association between tooth decay and anaerobic bacterial infection, then the decision on whether antibiotics covering anaerobic bacteria should be administered to treat aspiration pneumonia could be made based on an oral examination of the patient.

The use of proton pump inhibitors is also a recognized risk factor for aspiration pneumonia [34, 35], perhaps because these drugs increase gastric pH, which can allow the reflux of bacteria in the lower intestinal tract. The correct use of proton pump inhibitors is encouraged to avoid the increased risk of aspiration pneumonia, especially in older people.

5 Host Defense

When the host's defense system is functioning successfully, aspiration pneumonia is unlikely to develop even after the aspiration of highly virulent pathogens because of the cough reflex and the mucociliary clearance function. The clinical factors associated with compromise to the host's defense system against aspiration pneumonia are summarized in Table 8.3; advanced age, male sex, respiratory disease, and diabetes mellitus have been categorized as being supported by evidence level 2a, whereas malnutrition may fall into level 3b [7]. These factors are associated with the reduced ability to clear the pathogens by coughing or mucociliary transportation and with a weakened immune system less able to fight against the aspirated pathogens. Advanced age and malnutrition may weaken muscles associated with coughing. The impact of being of male sex can be confounded by other environmental factors, such as smoking and drinking alcohol. Population-based case–control studies have reported that current and past smoking for men and higher alcohol

Table 8.3 Host defensive factors associated with aspiration pneumonia risk

Affected function	Factor
Decreased mucociliary function and/or cough reflex	Advanced age
	Male sex
	Respiratory disease
	ACE/DD genotype
	Malnutrition
Weakened immune system	Diabetes mellitus
	Use of immunosuppressants

consumption are risk factors for community-acquired pneumonia [27, 36]. In addition, a history of regular exposure to gases, fumes, or chemicals at work might also contribute to the difference between the sexes [36]. This exposure predisposes workers to occupational respiratory diseases, which may weaken their mucociliary clearance systems.

Angiotensin-converting enzyme (ACE) inhibitor is a potential drug for preventing the development of aspiration pneumonia through acceleration of the cough reflex [37]. A recent meta-analysis reported that the ACE I/D polymorphism was associated with pneumonia risk but not with pneumonia mortality [38]. Takahashi et al. investigated how ACE inhibitor use and ACE genotypes related to the reduction of pneumonia risk in a Japanese elderly population [39]. They found that the use of an ACE inhibitor was beneficial for reducing the risk of pneumonia, particularly in individuals with the ACE genotypes ID and II.

There can be overlap between the host defense factors and aspiration risk factors. For example, advanced age and malnutrition are risk factors associated with both aspiration and the subsequent host defense [7]. Some other risk factors for aspiration pneumonia may also not be clearly classifiable as aspiration risk, pathogen-related factors, or factors associated with the host defense system.

The preexistence of a respiratory disease can potentially inhibit a patient's mucociliary function and the effective clearance of airway secretions by coughing [40, 41]. In addition, the treatment for the respiratory disease may itself result in the development of aspiration pneumonia. For example, inhaled steroid therapy for chronic respiratory diseases may result in a decline in local immunity, leaving the patient less able to fight against aspirated bacteria in the lower airways. It has been reported that inhaled steroid therapy for chronic obstructive pulmonary disease (COPD) is probably associated with increased risk for the development of pneumonia although not for pneumonia mortality [42–44]. The colonization of bacteria is more prevalent in patients with COPD, which may explain the adverse effects of inhaled steroid therapy [45]. For these reasons, current treatment guidelines for COPD do not recommend the routine use of inhaled steroids [46].

In addition to the decreased mucociliary function, COPD can leave patients susceptible to aspiration due to poor coordination between breathing and swallowing, cricopharyngeal muscle dysfunction, and changes in lung volume [47, 48]. Conditions related to other chronic respiratory diseases can also increase aspiration

risk; conversely, it has been reported that aspiration can in turn exacerbate the disease or its progression [47, 49–51]. Physicians should be aware of the impact of aspiration as part of a vicious cycle in chronic respiratory diseases.

6 Conclusions

This chapter reviewed the pathogenesis of aspiration pneumonia, focusing on aspiration risk and factors related to the pathogens and the host defense to clarify the differences and similarities between aspiration risk and aspiration pneumonia risk. The risk factors for aspiration are included among the risk factors for aspiration pneumonia, but the two sets of factors are not the same, and a focus on aspiration risk alone is insufficient for an understanding of the pathogenesis of aspiration pneumonia. Aspiration pneumonia risk is also associated with pathogen-related factors and conditions that compromise the host defense. All these factors should be considered for a better understanding of aspiration pneumonia and for formulating strategies to prevent not only aspiration but also the development of aspiration pneumonia.

References

1. Society TJR. The JRS guidelines for the management of pneumonia in adults. 2017. [in Japanese].
2. Komiya K, Ishii H, Kadota J. Healthcare-associated pneumonia and aspiration pneumonia. Aging Dis. 2015;6(1):27–37.
3. Marik PE, Kaplan D. Aspiration pneumonia and dysphagia in the elderly. Chest. 2003;124(1):328–36.
4. Sumi Y, Miura H, Michiwaki Y, Nagaosa S, Nagaya M. Colonization of dental plaque by respiratory pathogens in dependent elderly. Arch Gerontol Geriatr. 2007;44(2):119–24.
5. Scholthof KB. The disease triangle: pathogens, the environment and society. Nat Rev Microbiol. 2007;5(2):152–6.
6. Parrilla C, Valenza V, Calo L, Passali GC, Castaldi P, Galli J. Is it sufficient to quantify aspiration for predicting aspiration pneumonia? Clin Nucl Med. 2008;33(3):236–9.
7. van der Maarel-Wierink CD, Vanobbergen JN, Bronkhorst EM, Schols JM, de Baat C. Risk factors for aspiration pneumonia in frail older people: a systematic literature review. J Am Med Dir Assoc. 2011;12(5):344–54.
8. Mandell LA, Niederman MS. Aspiration pneumonia. N Engl J Med. 2019;380(7):651–63.
9. Sura L, Madhavan A, Carnaby G, Crary MA. Dysphagia in the elderly: management and nutritional considerations. Clin Interv Aging. 2012;7:287–98.
10. Cohen DL, Roffe C, Beavan J, Blackett B, Fairfield CA, Hamdy S, et al. Post-stroke dysphagia: a review and design considerations for future trials. Int J Stroke. 2016;11(4):399–411.
11. Hannawi Y, Hannawi B, Rao CP, Suarez JI, Bershad EM. Stroke-associated pneumonia: major advances and obstacles. Cerebrovasc Dis. 2013;35(5):430–43.
12. Barbon CE, Steele CM. Efficacy of thickened liquids for eliminating aspiration in head and neck cancer: a systematic review. Otolaryngol Head Neck Surg. 2015;152(2):211–8.

13. Nakagawa T, Sekizawa K, Nakajoh K, Tanji H, Arai H, Sasaki H. Silent cerebral infarction: a potential risk for pneumonia in the elderly. J Intern Med. 2000;247(2):255–9.
14. Xu Z, Gu Y, Li J, Wang C, Wang R, Huang Y, et al. Dysphagia and aspiration pneumonia in elderly hospitalization stroke patients: risk factors, cerebral infarction area comparison. J Back Musculoskelet Rehabil. 2019;32(1):85–91.
15. Takizawa C, Gemmell E, Kenworthy J, Speyer R. A systematic review of the prevalence of oropharyngeal dysphagia in stroke, Parkinson's disease, Alzheimer's disease, head injury, and pneumonia. Dysphagia. 2016;31(3):434–41.
16. Meyer KC. Gastroesophageal reflux and lung disease. Expert Rev Respir Med. 2015;9(4):383–5.
17. Bar-Sever Z. Scintigraphic evaluation of gastroesophageal reflux and pulmonary aspiration in children. Semin Nucl Med. 2017;47(3):275–85.
18. Teramoto S, Yamamoto H, Yamaguchi Y, Tmoita T, Ouchi Y. Diffuse aspiration bronchiolitis due to achalasia. Chest. 2004;125(1):349–50.
19. Manabe T, Teramoto S, Tamiya N, Okochi J, Hizawa N. Risk factors for aspiration pneumonia in older adults. PLoS One. 2015;10(10):e0140060.
20. Stevenson RD, Allaire JH. The development of normal feeding and swallowing. Pediatr Clin N Am. 1991;38(6):1439–53.
21. Steele CM, Cichero JA. Physiological factors related to aspiration risk: a systematic review. Dysphagia. 2014;29(3):295–304.
22. Sjogren P, Wardh I, Zimmerman M, Almstahl A, Wikstrom M. Oral care and mortality in older adults with pneumonia in hospitals or nursing homes: systematic review and meta-analysis. J Am Geriatr Soc. 2016;64(10):2109–15.
23. Yoneyama T, Yoshida M, Ohrui T, Mukaiyama H, Okamoto H, Hoshiba K, et al. Oral care reduces pneumonia in older patients in nursing homes. J Am Geriatr Soc. 2002;50(3):430–3.
24. Terpenning MS, Taylor GW, Lopatin DE, Kerr CK, Dominguez BL, Loesche WJ. Aspiration pneumonia: dental and oral risk factors in an older veteran population. J Am Geriatr Soc. 2001;49(5):557–63.
25. Scannapieco FA, Cantos A. Oral inflammation and infection, and chronic medical diseases: implications for the elderly. Periodontology. 2000;72(1):153–75.
26. Awano S, Ansai T, Takata Y, Soh I, Akifusa S, Hamasaki T, et al. Oral health and mortality risk from pneumonia in the elderly. J Dent Res. 2008;87(4):334–9.
27. Almirall J, Bolibar I, Serra-Prat M, Roig J, Hospital I, Carandell E, et al. New evidence of risk factors for community-acquired pneumonia: a population-based study. Eur Respir J. 2008;31(6):1274–84.
28. Tanner AC. Anaerobic culture to detect periodontal and caries pathogens. J Oral Biosci. 2015;57(1):18–26.
29. Sanz M, Beighton D, Curtis MA, Cury JA, Dige I, Dommisch H, et al. Role of microbial biofilms in the maintenance of oral health and in the development of dental caries and periodontal diseases. Consensus report of group 1 of the Joint EFP/ORCA workshop on the boundaries between caries and periodontal disease. J Clin Periodontol. 2017;44(Suppl 18):S5–S11.
30. Marsh PD. Microbial ecology of dental plaque and its significance in health and disease. Adv Dent Res. 1994;8(2):263–71.
31. Marik PE, Careau P. The role of anaerobes in patients with ventilator-associated pneumonia and aspiration pneumonia: a prospective study. Chest. 1999;115(1):178–83.
32. Bowerman TJ, Zhang J, Waite LM. Antibacterial treatment of aspiration pneumonia in older people: a systematic review. Clin Interv Aging. 2018;13:2201–13.
33. Bartlett JG. How important are anaerobic bacteria in aspiration pneumonia: when should they be treated and what is optimal therapy. Infect Dis Clin N Am. 2013;27(1):149–55.
34. Zirk-Sadowski J, Masoli JA, Delgado J, Hamilton W, Strain WD, Henley W, et al. Proton-pump inhibitors and long-term risk of community-acquired pneumonia in older adults. J Am Geriatr Soc. 2018;66(7):1332–8.

35. Lambert AA, Lam JO, Paik JJ, Ugarte-Gil C, Drummond MB, Crowell TA. Risk of community-acquired pneumonia with outpatient proton-pump inhibitor therapy: a systematic review and meta-analysis. PLoS One. 2015;10(6):e0128004.
36. Loeb M, Neupane B, Walter SD, Hanning R, Carusone SC, Lewis D, et al. Environmental risk factors for community-acquired pneumonia hospitalization in older adults. J Am Geriatr Soc. 2009;57(6):1036–40.
37. Rafailidis PI, Matthaiou DK, Varbobitis I, Falagas ME. Use of ACE inhibitors and risk of community-acquired pneumonia: a review. Eur J Clin Pharmacol. 2008;64(6):565–73.
38. Nie W, Zang Y, Chen J, Liu T, Xiao L, Xiu Q. Angiotensin-converting enzyme I/D polymorphism is associated with pneumonia risk: a meta-analysis. JRAAS. 2014;15(4):585–92.
39. Takahashi T, Morimoto S, Okaishi K, Kanda T, Nakahashi T, Okuro M, et al. Reduction of pneumonia risk by an angiotensin I-converting enzyme inhibitor in elderly Japanese inpatients according to insertion/deletion polymorphism of the angiotensin I-converting enzyme gene. Am J Hypertens. 2005;18(10):1353–9.
40. Tilley AE, Walters MS, Shaykhiev R, Crystal RG. Cilia dysfunction in lung disease. Annu Rev Physiol. 2015;77:379–406.
41. Ma J, Rubin BK, Voynow JA. Mucins, mucus, and goblet cells. Chest. 2018;154(1):169–76.
42. Festic E, Bansal V, Gupta E, Scanlon PD. Association of inhaled corticosteroids with incident pneumonia and mortality in COPD patients; systematic review and meta-analysis. COPD. 2016;13(3):312–26.
43. Ernst P, Saad N, Suissa S. Inhaled corticosteroids in COPD: the clinical evidence. Eur Respir J. 2015;45(2):525–37.
44. Yang M, Du Y, Chen H, Jiang D, Xu Z. Inhaled corticosteroids and risk of pneumonia in patients with chronic obstructive pulmonary disease: a meta-analysis of randomized controlled trials. Int Immunopharmacol. 2019;77:105950.
45. Leung JM, Tiew PY, Mac Aogain M, Budden KF, Yong VF, Thomas SS, et al. The role of acute and chronic respiratory colonization and infections in the pathogenesis of COPD. Respirology. 2017;22(4):634–50.
46. Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. GOLD executive summary. Am J Respir Crit Care Med. 2017;195(5):557–82.
47. Zheng Z, Wu Z, Liu N, Chen P, Hou P, Wang X, et al. Silent aspiration in patients with exacerbation of COPD. Eur Respir J. 2016;48(2):570–3.
48. Gross RD, Atwood CW Jr, Ross SB, Olszewski JW, Eichhorn KA. The coordination of breathing and swallowing in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2009;179(7):559–65.
49. Hou P, Deng H, Wu Z, Liu H, Liu N, Zheng Z, et al. Detection of salivary aspiration using radionuclide salivagram SPECT/CT in patients with COPD exacerbation: a preliminary study. J Thorac Dis. 2016;8(10):2730–7.
50. Ryerson CJ, Cottin V, Brown KK, Collard HR. Acute exacerbation of idiopathic pulmonary fibrosis: shifting the paradigm. Eur Respir J. 2015;46(2):512–20.
51. Gavini S, Borges LF, Finn RT, Lo WK, Goldberg HJ, Burakoff R, et al. Lung disease severity in idiopathic pulmonary fibrosis is more strongly associated with impedance measures of bolus reflux than pH parameters of acid reflux alone. Neurogastroenterol Motil. 2017;29(5):e13001.

Chapter 9
A Possible Association Between Oral Bacteria and Aspiration Pneumonia: Do Oral Bacteria Have Roles in the Pathogenesis of Aspiration Pneumonia?

Tomotaka Nishizawa

Abstract Saliva contains 10^8 bacteria per milliliter and more than 700 bacterial species. Although young, healthy individuals can clear these bacteria from the lungs if saliva is aspirated, elderly or immunocompromised individuals cannot and may develop aspiration pneumonia as a result. The microbiota in saliva comes from the oral mucosa, tongue, and teeth, with the flora of the tongue being most similar to the salivary flora. The bacterial composition of the tongue flora is associated with the prognosis of pneumonia. In addition, the thick dental biofilm, and especially the subgingival biofilm, is rich in obligate anaerobic bacteria that cause periodontal disease. Mice infected with a mixture of these bacteria have increased inflammatory cytokines and increased mortality from pneumonia. In addition to specific bacterial species, the absolute number of bacteria in the oral cavity affects the development of pneumonia. Oral care is therefore important for prevention of aspiration pneumonia. An Oral Health Assessment Tool allows dentists or non-specialists to identify declining oral health and may help to identify patients at risk for aspiration pneumonia.

Keywords Oral bacteria · Dental biofilm · Tongue flora

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1 Introduction

Many bacterial species inhabiting the oral cavity are believed to cause aspiration pneumonia, and it is difficult to selectively decrease these specific bacteria [1]. Some of the oral bacteria are swallowed with saliva. When the saliva is aspirated by healthy individuals and enters the respiratory tract, it is cleared by the bronchial ciliated epithelium and macrophages. However, in immunocompromised individuals and the elderly, aspiration of oral bacteria is a risk factor for pneumonia, even if the bacteria do not commonly cause pneumonia. Elderly people have a high rate of swallowing problems and are more likely to aspirate saliva than younger individuals. Therefore, oral bacteria are more likely to be involved in the onset of pneumonia in elderly people than in younger, healthier individuals.

2 Saliva and Oral Flora

Many bacteria colonize the human body. Nearly 1×10^8 bacteria are present in every milliliter of saliva, representing more than 700 bacterial species. The oral cavity is an unusual environment, because it is covered with mucous membranes, and the teeth erupt through these membranes. The oxygen concentration on the buccal side of the molar teeth is about 5% of that in the atmosphere. In addition, the mucosa is constantly perfused by saliva containing antimicrobial substances, such as lysozyme, lactoferrin, and peroxidase. In addition, the temperature of the oral cavity fluctuates between 15.4 °C and 68.0 °C as cold and hot foods are consumed. Because the oral cavity is a special environment, its bacterial flora is also unique but differs between sites within the cavity. In many locations, including the oral cavity, bacteria form biofilms, which are aggregates of bacteria surrounded by polysaccharides and other molecules produced by the bacteria. Because the oral mucosa peels off periodically as the epithelium grows, its biofilm is thin, and the number of cells is small. In contrast, because the tooth surface does not peel off, bacteria easily grow and a thick biofilm is formed. This is called dental plaque and is the most analyzed of the bacterial flora. Dental plaque includes supragingival and subgingival types. Differences between these types reflect environmental differences such as oxygen concentration. Bacterial species that have colonized subgingival plaques have a greater proportion of obligate anaerobic bacteria, including periodontal disease bacteria, than supragingival plaques. The tongue has papillae on its surface as well as other surface irregularities. Therefore, a larger number of bacteria can settle on the tongue than on the oral mucosa, and a thick biofilm is formed.

Saliva is sterile when secreted from cells of the salivary glands, but in the oral cavity, it is contaminated with bacteria released from the biofilms on the oral mucosa, tongue, and teeth. Therefore, the flora in saliva depends on the state of oral hygiene. In particular, the formation of thick biofilms on the tongue and teeth affects the salivary flora. However, the salivary flora is more similar to the tongue flora than

to the supragingival and subgingival dental plaque, so that the tongue surface biofilm is considered to be the most important factor affecting the bacterial composition of the saliva.

3 Microaspiration and Pneumonia

Elderly people with reduced salivary reflex may have clinically silent aspiration while sleeping. To clarify the relationship between saliva and aspiration pneumonia, it is necessary to prove that saliva is actually aspirated and reaches the lungs.

Kikuchi et al. studied inapparent aspiration by using indium chloride as a tracer and reported a significantly higher percentage of inapparent aspiration among patients with a history of acute pneumonia (71%) than in a control group (10%) [2]. These data suggest that we should provide more intensive oral care to patients at risk to prevent aspiration pneumonia.

Patients with dysphagia without associated coughing without subjective symptoms are known to have reduced cough reflex. This reflex abnormality is related to a decrease in substance P, which regulates the cough reflex [3, 4]. Substance P is a peptide that is synthesized in response to the stimulation of dopamine in the brain and is secreted into the pharynx and trachea [5, 6]. In the elderly and patients with cerebrovascular disorders, cerebral blood flow is decreased, which leads to reduction in substance P [7]. Arai and colleagues found a decrease in blood substance P levels in 16 patients with hypertension and asymptomatic dysphagia. However, the administration of an ACE inhibitor for the purpose of suppressing the degradation of substance P improves the dysphagia disorders in 10 patients. In addition, eight of 10 were reported to have elevated blood levels of substance P [8, 9].

4 Do Oral Bacteria Have Roles in the Pathogenesis of Aspiration Pneumonia?

Nine studies have been published on the isolation of bacteria from aspiration pneumonia lesions (Table 9.1). The bacterial species that have been isolated include pneumonia-causing bacteria such as *Streptococcus pneumoniae* and *Klebsiella pneumoniae*. In addition to the pneumonia-inducing group, the isolation of streptococci including *S. mitis* and *S. salivarius* and of obligate anaerobic bacteria derived from the oral cavity, such as *Bacteroides melaninogenicus* and *Fusobacterium*, *Peptococcus*, *Peptostreptococcus,* and *Veillonella* species, has been reported.

The bacterial species described as *B. melaninogenicus* is a past taxonomic name that includes bacterial species such as those now named *Porphyromonas gingivalis* and *Prevotella intermedia*, which are pathogens of chronic periodontitis. These bacterial species increase in subgingival plaque as periodontitis progresses. Therefore,

Table 9.1 Pathogens involved in aspiration pneumonia

Study	Year	Percent of patients with anaerobic infection (alone (%)/ mixed (%)/total (%))	Most common anaerobes	Most common aerobes
Bartlett	1975	46/41/87	*Bacteroides sp* *Fusobacterium sp* *Peptostreptococcus sp*	*Streptococcus pneumoniae* *Staphylococcus aureus* *K pneumoniae*
Bartlett	1974	46/46/92	*Bacteroides sp* *Fusobacterium sp* *Peptostreptococcus sp*	*Staphylococcus aureus* *Streptococcus pneumoniae* *Klebsiella sp* *Pseudomonas aeruginosa* *E coli*
Cesar	1975	35/65/100	*Bacteroides sp* *Fusobacterium sp* *Propionibacterium*	*S pneumoniae* *Haemophilus influenzae* *α-Hemolytic Streptococcus*
Lorber	1974	32/30/62	*Fusobacterium sp* *Peptostreptococcus sp* *Peptococcus sp*	*Streptococcus sp* *P aeruginosa* *E coli*
Brook	1980	3/91/94	*Bacteroides sp* *Peptococcus sp* *Peptostreptococcus sp* *Fusobacterium sp*	*α-Hemolytic Streptococcus* *P aeruginosa* *S pneumoniae*
El-Solh	2003	20/11/31	*Prevotella sp* *Fusobacterium sp*	*E coli* *K pneumoniae* *S aureus*
Tokuyasu	2009	Not reported/not reported/27	*Fusobacterium sp* *Streptococcus sp* *Peptococcus sp*	*Streptococcus agalactiae* *Methicillin-resistant Staphylococcus aureus* *K pneumoniae*
Takayanagi	2010	12/14/26	*Peptostreptococcus sp* *Prevotella sp* *Fusobacterium sp* *Veillonella sp*	*Streptococcus mitis* *Streptococcus constellatus* *Streptococcus salivarius*
Wang	2005	13/44/57	*Peptostreptococcus sp* *Prevotella sp* *Bacteroides sp*	*K. pneumoniae* *Streptococcus milleri* *Viridans streptococci*

Adapted from [10]

when oral hygiene is poor and periodontitis worsens after middle age, these bacterial species increase in saliva. *Staphylococcus aureus* and *Pseudomonas aeruginosa* are also found in the oral cavity, although their numbers are small. When these bacterial species are detected in pneumonia, they are considered to be derived from saliva. It may indicate that oral bacteria transferred to the lower respiratory tract by aspiration of saliva are involved in pneumonia.

Shinzato et al. reported that *S. anginosus* strains and obligate anaerobic bacteria were detected in 45 patients with pneumonia and lung abscess and 25 patients with chest abscess. Experiments with mice infected with a mix of *S. constellatus* and *P. intermedia* showed that mixed infection of streptococci and obligate anaerobic bacteria enhanced pathogenicity compared with single infection [11]. In addition, compared with infection with *P. gingivalis* alone, more inflammatory cytokines were observed in mice with a mixed infection of *P. gingivalis* and *Treponema denticola*, and the mixed infection increased the mortality of the mice due to pneumonia [12]. The increased pathogenicity with mixed infection is consistent with pneumonia occurring due to the influx of saliva containing multiple bacterial species into the lower respiratory tract.

Benedyk et al. created a mouse pneumonia model using *P. gingivalis. P. gingivalis* produces a group of cysteine proteases called gingipains that act as virulence factors [13]. The number of *P. gingivalis* bacteria found in the lung was the same in the wild-type strain and a gingipain-deficient strain, indicating that gingipain is not required for colonization of the lung. However, the gingipain-deficient strains did not show alveolar hemorrhage, necrosis, or neutrophil infiltration nor increased expression of TNF (Tumor Necrosis Factor), IL-6, IL-17, or CRP (C-reactive protein). In contrast, the wild-type strain had increased expression of IL-17, blood platelet count, and platelet activity in the lung, and the mortality rate of the mice was high. *Prevotella* species that are often isolated from pneumonia also produce similar extracellular proteases that are thought to be involved in the pathogenesis [14].

5 Oral Bacterial Counts, Oral Care, and the Oral Health Assessment Tool

One important risk factor for aspiration pneumonia is oral health [15]. In 2016, the Japanese Society of Gerontology and Geriatrics proposed that elderly people suffer from oral dysfunction due to problems in seven areas: inadequate oral hygiene, dry mouth, reduced occlusal force, decreased tongue and lip movement, low tongue pressure, reduced chewing, and reduced swallowing. The prevalence of oral dysfunction increases after the age of 50 and affects about half of those in their 50s, indicating that oral function actually declines before people become elderly [16].

Poor oral hygiene is measured by counting the number of bacteria in the oral cavity using the dielectrophoretic impedance measurement system [17, 18], with 6.5 log 10 CFU/ml or more defined as poor oral hygiene. In a previous study [18], pneumonia was found to occur even when the number of oral bacteria was low, but the incidence was significantly higher when the concentration was 8.5 log 10 (CFU/ml) or more. Recently, a simple, 1-min evaluation of the number of oral bacteria has been developed. To collect the oral bacterial sample, we scratch the center of the tongue back using a sterile cotton swab attached to a constant pressure specimen collection device according to the manufacturer's instruction (PHC Ltd., Tokyo, Japan) [19]. For the analysis, we used a bacterial count-measuring instrument

(bacteria counter PHC Ltd., Tokyo, Japan) [17]. This instrument collects bacteria in a liquid on an electrode, measures the change in impedance, and converts it into a bacterial concentration (CFU/ml) in 1 ml of sample. Using this measurement method, it has been reported that the high number of oral bacteria in the elderly is related to the incidence of pneumonia [18].

Oral care, particularly by dentists and dental hygienists, has been reported to reduce bacteria and to suppress the development of pneumonia [20, 21]. However, individuals under nursing care at home or in a care facility may not have access to specialists to perform oral care, so it is important to standardize oral care procedures and to objectively evaluate the quality of oral care. The Oral Health Assessment Tool (OHAT) is a candidate for an index that can objectively evaluate the state of the oral cavity without using special equipment. OHAT visually assesses eight items: lips, tongue, gingiva/mucosa, saliva, remaining teeth, dentures, oral cleansing, and toothache. Each item is given a score of 0 (healthy), 1 (changes), or 2 (unhealthy). Thus, OHAT is used to visually evaluate not only the cleanliness of the mucous membranes but also mastication-related items such as the use of dentures, the presence or absence of fracture, and the number of caries. Non-dentists can perform the evaluation, and OHAT is used in the field of swallowing rehabilitation, but to date no reports have been used to assess the risk of aspiration pneumonia.

OHAT is reliable and valid and is significantly correlated with other oral hygiene assessment tools. Nishizawa et al. showed that oral health as assessed with OHAT has high diagnostic value for assessing the risk of aspiration pneumonia and that the number of bacteria can be reduced by oral care [22]. The Revised Oral Assessment Guide (ROAG) has been widely used in the field of nursing care as a tool for oral assessment [23], but OHAT is more precise than ROAG in terms of assessing the state of cleaning in the oral cavity, and it also evaluates the remaining teeth and dentures as separate items. Therefore, OHAT is superior to ROAG for evaluations related to the oral phase of swallowing [24] and is highly valued in the field of swallowing rehabilitation.

6 Tongue Flora and Risk Assessment

Oral care that reduces the number of bacteria in saliva suppresses the incidence and delays the onset of aspiration pneumonia. A study on the tongue flora and risk assessment of aspiration pneumonia has been reported, applying the similarity of the tongue-back flora to bacteria in saliva. Kageyama and colleagues report that the tongue flora can be divided into two types: In type I, *Prevotella* and *Veillonella* species are the major components, and in type II, *Neisseria* and *Fusobacterium* are the most common. Participants with type I tongue flora had a higher risk of all-cause death (corrected hazard ratio of 3.79, 95% CI: 1.38–10.39) and pneumonia-related death (corrected hazard ratio of 13.88, 95% CI: 1.64–117.21) as compared with those who had type II tongue flora (Fig. 9.1), underscoring the important role of tongue bacteria in aspiration pneumonia [25].

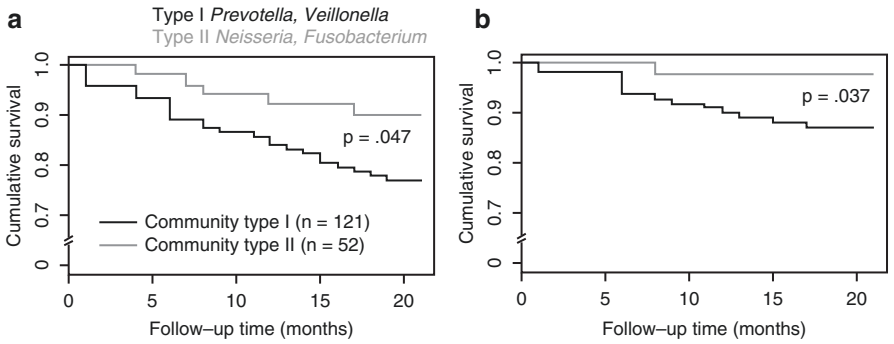

Fig. 9.1 Survival plots of each community type (Type I Prevotella, Veillonella, Type II Neisseria, Fusobacterium) by (**a**) all-cause death, (**b**) pneumonia-related death. Left Figure (**a**) and Right Figure (**b**) In the Kaplan–Meier survival analysis, subjects with type I microbiota bore significant associations with all-cause (p = 0.047) and pneumonia-related deaths (p = 0.037), compared to those with type II microbiota

7 Conclusion

In recent years, it has become possible to comprehensively capture bacteria in the oral cavity. It is becoming possible to analyze which bacterial group among many pathogens is involved in aspiration pneumonia. Future analysis is expected to establish a means to prevent aspiration pneumonia by identifying patients in need of appropriate oral care on the basis of risk determination data.

References

1. Mandell LA, Niederman MS. Aspiration pneumonia. N Engl J Med. 2019;380(7):651–63. https://doi.org/10.1056/NEJMra1714562.
2. Kikuchi R, Watabe N, Konno T, Mishina N, Sekizawa K, Sasaki H. High incidence of silent aspiration in elderly patients with community-acquired pneumonia. Am J Respir Crit Care Med. 1994;150(1):251–3. https://doi.org/10.1164/ajrccm.150.1.8025758.
3. Ohrui T. Preventive strategies for aspiration pneumonia in elderly disabled persons. Tohoku J Exp Med. 2005;207(1):3–12.
4. Yamaya M, Yanai M, Ohrui T, Arai H, Sasaki H. Interventions to prevent pneumonia among older adults. J Am Geriatr Soc. 2001;49(1):85–90.
5. Nakagawa T, Ohrui T, Sekizawa K, Sasaki H. Sputum substance P in aspiration pneumonia. Lancet. 1995;345(8962):1447.
6. Mutoh T, Bonham AC, Joad JP. Substance P in the nucleus of the solitary tract augments bronchopulmonary C fiber reflex output. Am J Physiol Regul Integr Comp Physiol. 2000;279(4):R1215–23. https://doi.org/10.1152/ajpregu.2000.279.4.R1215.
7. Mistrova E, Kruzliak P, Chottova DM. Role of substance P in the cardiovascular system. Neuropeptides. 2016;58:41–51. https://doi.org/10.1016/j.npep.2015.12.005.

8. Arai T, Yasuda Y, Takaya T, Toshima S, Kashiki Y, Yoshimi N, et al. ACE inhibitors and symptomless dysphagia. Lancet. 1998;352(9122):115–6. https://doi.org/10.1016/s0140-6736(98)85021-6.
9. Arai T, Yasuda Y, Toshima S, Yoshimi N, Kashiki Y. ACE inhibitors and pneumonia in elderly people. Lancet. 1998;352(9144):1937–8. https://doi.org/10.1016/s0140-6736(05)60437-0.
10. DiBardino DM, Wunderink RG. Aspiration pneumonia: a review of modern trends. J Crit Care. 2015;30(1):40–8. https://doi.org/10.1016/j.jcrc.2014.07.011.
11. Shinzato T, Saito A. The *Streptococcus milleri* group as a cause of pulmonary infections. Clin Infect Dis. 1995;21(Suppl 3):S238–43. https://doi.org/10.1093/clind/21.supplement_3.s238.
12. Kimizuka R, Kato T, Ishihara K, Okuda K. Mixed infections with *Porphyromonas gingivalis* and *Treponema denticola* cause excessive inflammatory responses in a mouse pneumonia model compared with monoinfections. Microbes Infect. 2003;5(15):1357–62. https://doi.org/10.1016/j.micinf.2003.09.015.
13. Benedyk M, Mydel PM, Delaleu N, Plaza K, Gawron K, Milewska A, et al. Gingipains: critical factors in the development of aspiration pneumonia caused by *Porphyromonas gingivalis*. J Innate Immun. 2016;8(2):185–98. https://doi.org/10.1159/000441724.
14. Huffnagle GB, Dickson RP, Lukacs NW. The respiratory tract microbiome and lung inflammation: a two-way street. Mucosal Immunol. 2017;10(2):299–306. https://doi.org/10.1038/mi.2016.108.
15. Quagliarello V, Ginter S, Han L, Van Ness P, Allore H, Tinetti M. Modifiable risk factors for nursing home-acquired pneumonia. Clin Infect Dis. 2005;40(1):1–6. https://doi.org/10.1086/426023.
16. Minakuchi S, Tsuga K, Ikebe K, Ueda T, Tamura F, Nagao K, et al. Oral hypofunction in the older population: position paper of the Japanese society of gerodontology in 2016. Gerodontology. 2018;35(4):317–24. https://doi.org/10.1111/ger.12347.
17. Kikutani T, Tamura F, Takahashi Y, Konishi K, Hamada R. A novel rapid oral bacteria detection apparatus for effective oral care to prevent pneumonia. Gerodontology. 2012;29(2):e560–5. https://doi.org/10.1111/j.1741-2358.2011.00517.x.
18. Kikutani T, Tamura F, Tashiro H, Yoshida M, Konishi K, Hamada R. Relationship between oral bacteria count and pneumonia onset in elderly nursing home residents. Geriatr Gerontol Int. 2015;15(4):417–21. https://doi.org/10.1111/ggi.12286.
19. Hamada R, Suehiro J, Nakano M, Kikutani T, Konishi K. Development of rapid oral bacteria detection apparatus based on dielectrophoretic impedance measurement method. IET Nanobiotechnol. 2011;5(2):25–31. https://doi.org/10.1049/iet-nbt.2010.0011.
20. Yoneyama T, Yoshida M, Ohrui T, Mukaiyama H, Okamoto H, Hoshiba K, et al. Oral care reduces pneumonia in older patients in nursing homes. J Am Geriatr Soc. 2002;50(3):430–3.
21. Ames NJ, Sulima P, Yates JM, McCullagh L, Gollins SL, Soeken K, et al. Effects of systematic oral care in critically ill patients: a multicenter study. Am J Crit Care. 2011;20(5):e103–14. https://doi.org/10.4037/ajcc2011359.
22. Nishizawa T, Niikura Y, Akasaka K, Watanabe M, Kurai D, Amano M, et al. Pilot study for risk assessment of aspiration pneumonia based on oral bacteria levels and serum biomarkers. BMC Infect Dis. 2019;19(1):761. https://doi.org/10.1186/s12879-019-4327-2.
23. Andersson P, Hallberg IR, Renvert S. Inter-rater reliability of an oral assessment guide for elderly patients residing in a rehabilitation ward. Spec Care Dentist. 2002;22(5):181–6.
24. Simpelaere IS, Van Nuffelen G, Vanderwegen J, Wouters K, De Bodt M. Oral health screening: feasibility and reliability of the oral health assessment tool as used by speech pathologists. Int Dent J. 2016;66(3):178–89. https://doi.org/10.1111/idj.12220.
25. Kageyama S, Takeshita T, Furuta M, Tomioka M, Asakawa M, Suma S, et al. Relationships of variations in the tongue microbiota and pneumonia mortality in nursing home residents. J Gerontol A Biol Sci Med Sci. 2018;73(8):1097–102. https://doi.org/10.1093/gerona/glx205.

Chapter 10
The Role of Anaerobes on the Pathogenesis of Aspiration Pneumonia: Anaerobes May Be Involved in the Pathogenesis?

Masaki Ishii

Abstract Aspiration pneumonia (AP) is a pulmonary infection caused by aspiration of substances from the laryngopharynx or upper gastrointestinal tract, and substances involved in aspiration include oropharyngeal secretions, saliva, food resides, or bacteria. There are more than 700 types of microorganisms in the human oral cavity, and the bacterial species change depending on the environment in the oral cavity. The percentage of anaerobic bacterium reportedly increases when oral hygiene deteriorates. The relationship between anaerobic bacterium in the oral cavity and AP has been known for a long time; however, the influence of anaerobic bacteria on AP has not been fully clarified in clinical studies. Furthermore, there is a lack of quality evidence for the causative agents in AP. There were many reports in the 1970s that anaerobic bacteria were mainly involved in AP, but recent reports indicate that anaerobic bacterium may be less involved in AP than previously reported. The interpretation of the anaerobic bacterial involvement in AP has changed over time and past reports may contain various biases. Clinical studies indicate that, although anaerobic bacterium is considered to be a causative bacterium of AP, it has not been established that they are the main pathogens of AP. Thus, at this time, it is difficult to clearly define the role of anaerobes in AP.

Keywords Aspiration pneumonia · Anaerobic bacterium · Causal bacterium

1 Introduction

Pneumonia is the fourth leading cause of death in Japan, with elderly people accounting for most of the cases. The proportion of aspiration pneumonia (AP) in all pneumonia increases with age. Teramoto et al. reported that 80% of hospitalized

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patients with pneumonia aged >70 years had aspiration and that 60.1% of cases of community-acquired pneumonia (CAP) and 86.7% of hospital-acquired pneumonia (HAP) cases involved aspiration [1]. Aspiration is defined as a foreign substance entering the airway beyond the vocal cords, and in general, aspiration substances are oropharyngeal secretions, saliva, bacteria, and food residues [2, 3]. This section describes the role of anaerobic bacteria in AP.

2 Pathogenesis of Aspiration Pneumonia

Aspiration pneumonia is a pulmonary infection caused by aspiration of substances from the laryngopharynx or upper gastrointestinal tract. In general, even if aspiration presents, pneumonia does not occur if the patient's body defense functions such as cough reflex, airway ciliary movement, and immune function are normal. However, AP can develop when the defense functions are lessened, there is a large amount of aspiration substance or the toxicity of the aspiration of substances is high [2]. In elderly people with neurological disorders or are bedridden, aspiration is likely to occur due to reduced cough reflexes and swallowing function, and the bacteria that cause pneumonia are likely to increase due to deteriorated oral hygiene. In general, most of the causative agents of CAP are *pneumococci*, *Haemophilus influenzae*, and mycoplasma; however, causes of AP are reported to be anaerobic bacteria that are mainly present in the oral cavity [4–6]. A study in the Japanese elderly has shown that sputum aspiration, reduced swallowing function, dehydration, and dementia were risk factors for AP [7]. We have also reported that sleep apnea syndrome is a risk factor for lower respiratory tract infection in elderly residents in long-term care facilities in Japan [8]. This may be due to changes in the oral bacterial flora associated with dry mouth. Aspiration may be completely asymptomatic or present with signs or symptoms, and elderly people often remain asymptomatic aspiration [2, 3]. In general, elderly people are more likely to develop AP and, even after recovery, AP is likely to recur.

3 Oral Bacterial Flora

There are more than 700 types of microorganisms in the human oral cavity [9]. The number of microorganisms is kept constant in the oral cavity in which teeth, oral mucosa, and saliva are present, and the indigenous bacteria suppress the growth of pathogenic bacterium [10]. Indigenous bacteria form bacterial flora on the tooth surface or in the oral mucosa and coexist with various other bacteria [9, 10]. When the bacterial flora in the oral cavity changes due to aging or deterioration of the general condition, increases in pathogenic bacteria in the oral cavity are likely to cause disease in various organs. According to statistics from the Ministry of Health, Labour, and Welfare in Japan, in 2017, the total number of patients with gingival and

periodontal diseases was about 4 million, and the prevalence increases with age [11]. The periodontal pocket between the teeth and the gingiva is the main colonization site for oral bacterium, and aerobic bacteria are found predominantly near the entrance of the periodontal pocket while anaerobic bacteria are found more deep in the pocket [12, 13]. Periodontal disease is thought to be largely related to anaerobic gram-negative bacilli isolated from plaque [14]. It has also been reported that the bacterial species vary depending on the environment in the oral cavity, and anaerobic bacteria increase when oral hygiene deteriorates [15]. In a study comparing age-matched controls with elderly residents in long-term care facilities, Russell et al. found that colonization of respiratory pathogens in the oral cavity was 0% in controls and 14% in elderly residents in long-term care facilities [16]. Yoneyama et al. reported that the elderly receiving oral care had lower incidence of fever and mortality compared to controls not receiving oral care [17]. These reports indicate the possibility of oral bacterial flora having an effect on respiratory disease even though these studies were mainly from the viewpoint of the oral environment or oral care.

4 Treatment Guideline for Respiratory Infections

The JAID/JSC infectious disease treatment guideline by the Japanese Association for Infectious Diseases (JAID) and the Japanese Society of Chemotherapy (JSC) indicates that the cause of AP is related to *Streptococcus pneumoniae*, *Staphylococcus aureus, Klebsiella pneumoniae, Streptococcus anginosus* spp., and oral resident bacteria including anaerobic bacteria [18]. However, there is no clear statement that anaerobic bacteria are mainly involved in AP. The guideline indicates that antibacterial agents against AP should include drugs that are effective against both aerobic and anaerobic bacteria and does not indicate a selection of drugs that specifically focus on anaerobic bacteria [18]. The Executive Summary on AP in the guideline states that "the choice of penicillin drugs containing β-lactamase inhibitors is sufficient because they are caused by indigenous bacterium in the oral cavity including anaerobic bacterium," and the evidence level for this recommendation was determined to be B-II [18]. Evidence-level B-II is a general recommendation (B) (not a strong recommendation) based on data from non-randomized controlled trials (II). This recommendation indicates that anaerobic bacteria are considered to be a causative agent of AP but does not indicate that anaerobic bacteria are mainly involved in AP. In addition, this is based on non-RCT data, indicating that there is a lack of qualifying evidence.

5 Anaerobic Bacterium and Aspiration Pneumonia

In clinical studies, the influence of anaerobic bacteria on AP has not been fully clarified. Kadowaki et al. reported that the proportion of bacteria identified from sputum samples from 100 patients with AP was 48.1% for Gram-negative bacilli and 40.7%

for Gram-positive bacilli, and no anaerobic bacteria were identified [19]. Tokuyasu et al. reported that sputum samples from patients with AP collected by bronchoscopy were identified to be 51.6% Gram-negative bacilli and 27.4% anaerobes [20]. Furthermore, Ott et al. reported AP specimens from patients were 40.6% Gram-positive bacteria and 59.6% Gram-negative bacteria, and no anaerobic bacteria were found [21]. These results may be biased due to contamination from other bacteria during the process of specimen collection, difficulty in culturing anaerobic bacteria, or the administration of antibacterial drugs before specimen collection [22]. On the other hand, Son et al. have noted changes over time in the reporting on the bacterial cause of AP [23]. There were many reports that anaerobic bacteria were mainly involved in AP in the 1970s [24–26], but recent reporting shows that anaerobic bacteria are less involved in AP [20, 27–30]. In 2016, Akata et al. reported that oral streptococci were most frequently (31.0%) detected in patients with AP in a bacterial flora analysis targeting the 16S rRNA gene using bronchoalveolar lavage fluid directly collected from pneumonia lesions. They also found the percentage of anaerobic bacteria detected was 6.0% in patients with AP and 17.9% in patients with non-AP [31]. Considering the above, at the least, there is no clear evidence that anaerobic bacteria are the main pathogens of AP.

6 Conclusion

AP is a pulmonary infection caused by aspiration, and anaerobic bacteria in the oral cavity have been pointed to as the causal bacteria. However, past reports may be biased and there is not enough evidence to determine the bacterial causative agents of AP. At this time, it is difficult to clearly define the role of anaerobes in AP. However, it is clear that AP is greatly involved in the cause of death in the elderly, and it is an important issue in the future to establish evidence on the causative bacteria for AP in order to provide the most effective treatment.

References

1. Teramoto S, Fukuchi Y, Sasaki H, Sato K, Sekizawa K, Matsuse T, et al. High incidence of aspiration pneumonia in community- and hospital-acquired pneumonia in hospitalized patients: a multicenter, prospective study in Japan. J Am Geriatr Soc. 2008;56:577–9.
2. Marik PE. Aspiration pneumonitis and aspiration pneumonia. N Engl J Med. 2001;344:665–71.
3. Zaloga GP. Aspiration-related illnesses: definitions and diagnosis. JPEN. 2002;26:S2–7; discussion S7–8
4. Terpenning MS, Taylor GW, Lopatin DE, Kerr CK, Dominguez BL, Loesche WJ. Aspiration pneumonia: dental and oral risk factors in an older veteran population. J Am Geriatr Soc. 2001;49:557–63.
5. Preston AJ, Gosney MA, Noon S, Martin MV. Oral flora of elderly patients following acute medical admission. Gerontology. 1999;45:49–52.

6. Shay K. Infectious complications of dental and periodontal diseases in the elderly population. Clin Infect Dis. 2002;34:1215–23.
7. Manabe T, Teramoto S, Tamiya N, Okochi J, Hizawa N. Risk factors for aspiration pneumonia in older adults. PLoS One. 2015;10:e0140060.
8. Ishii M, Yamaguchi Y, Yamamoto H, Ouchi Y, Osumi S, Nakamura T. Relationship between sleep apnea and respiratory infections in bedridden elderly individuals on tube feeding. J Am Geriatr Soc. 2012;60:790–2.
9. Kolenbrander PE, Palmer RJ Jr, Rickard AH, Jakubovics NS, Chalmers NI, Diaz PI. Bacterial interactions and successions during plaque development. Periodontology. 2000;42:47–79.
10. Tada A, Senpuku H, Motozawa Y, Yoshihara A, Hanada N, Tanzawa H. Association between commensal bacteria and opportunistic pathogens in the dental plaque of elderly individuals. Clin Microbiol Infect. 2006;12:776–81.
11. e-Stat: Portal site of official statistics of Japan. Patient survey in 2017. https://www.e-stat.go.jp/
12. Ogawa T. Influence of bacteria on the universal. Mod Media. 2017;63:179–85. (in Japanese)
13. Loesche WJ, Gusberti F, Mettraux G, Higgins T, Syed S. Relationship between oxygen tension and subgingival bacterial flora in untreated human periodontal pockets. Infect Immun. 1983;42:659–67.
14. Yanagisawa H. Distribution of periodontal disease-related bacterial species using genetic testing method. J Jpn Soc Clin Microbiol. 2018;28:249–53. (in Japanese)
15. Imatani T, Ishihara K, Kato T, Okuda K. Effectiveness of oral bacterial control on prophylaxis of respiratory infection in elderly needing daily care. J Tokyo Dent Coll Soc. 1999;99:1097–101. (in Japanese)
16. Russell SL, Boylan RJ, Kaslick RS, Scannapieco FA, Katz RV. Respiratory pathogen colonization of the dental plaque of institutionalized elders. Spec Care Dentist. 1999;19:128–34.
17. Yoneyama T, Yoshida M, Matsui T, Sasaki H. Oral care and pneumonia. Oral care working group. Lancet. 1999;354:515.
18. JAID/JSC infection treatment guideline committee. Respiratory infection working group. JAID/JSC infection treatment guideline. Jpn J Chemother. 2014;62:1–109.
19. Kadowaki M, Demura Y, Mizuno S, Uesaka D, Ameshima S, Miyamori I, et al. Reappraisal of clindamycin IV monotherapy for treatment of mild-to-moderate aspiration pneumonia in elderly patients. Chest. 2005;127:1276–82.
20. Tokuyasu H, Harada T, Watanabe E, Okazaki R, Touge H, Kawasaki Y, et al. Effectiveness of meropenem for the treatment of aspiration pneumonia in elderly patients. Intern Med. 2009;48:129–35.
21. Ott SR, Allewelt M, Lorenz J, Reimnitz P, Lode H, German Lung Abscess Study Group. Moxifloxacin vs ampicillin/sulbactam in aspiration pneumonia and primary lung abscess. Infection. 2008;36:23–30.
22. Bowerman TJ, Zhang J, Waite LM. Antibacterial treatment of aspiration pneumonia in older people: a systematic review. Clin Interv Aging. 2018;13:2201–13.
23. Son YG, Shin J, Ryu HG. Pneumonitis and pneumonia after aspiration. J Dent Anesth Pain Med. 2017;17:1–12.
24. Bartlett JG, Gorbach SL, Finegold SM. The bacteriology of aspiration pneumonia. Am J Med. 1974;56:202–7.
25. Cesar L, Gonzalez C, Calia FM. Bacteriologic flora of aspiration-induced pulmonary infections. Arch Intern Med. 1975;135:711–4.
26. Bartlett JG, Gorbach SL. Treatment of aspiration pneumonia and primary lung abscess: penicillin g vs clindamycin. JAMA. 1975;234:935–7.
27. El-Solh AA, Pietrantoni C, Bhat A, Aquilina AT, Okada M, Grover V, et al. Microbiology of severe aspiration pneumonia in institutionalized elderly. Am J Respir Crit Care Med. 2003;167:1650–4.
28. Takayanagi N, Kagiyama N, Ishiguro T, Tokunaga D, Sugita Y. Etiology and outcome of community-acquired lung abscess. Respiration. 2010;80:98–105.

29. Wang JL, Chen KY, Fang CT, Hsueh PR, Yang PC, Chang SC. Changing bacteriology of adult community-acquired lung abscess in Taiwan: *Klebsiella pneumoniae* versus anaerobes. Clin Infect Dis. 2005;40:915–22.
30. Lobo LJ, Reed KD, Wunderink RG. Expanded clinical presentation of community-acquired methicillin-resistant *Staphylococcus aureus* pneumonia. Chest. 2010;138:130–6.
31. Akata K, Yatera K, Yamasaki K, Kawanami T, Naito K, Noguchi S, et al. The significance of oral streptococci in patients with pneumonia with risk factors for aspiration: the bacterial floral analysis of 16S ribosomal RNA gene using bronchoalveolar lavage fluid. BMC Pulm Med. 2016;16:79.

Chapter 11
Diffuse Aspiration Bronchiolitis and Post-gastrectomy Aspiration Pneumonia: Are There Special Forms of Aspiration Pneumonia Due to Aging and Gastrectomy?

Hiroshi Yamamoto

Abstract Aspiration pulmonary diseases can be classified into four categories: aspiration pneumonia, Mendelson's syndrome, diffuse aspiration bronchiolitis (DAB), and post-gastrectomy aspiration pneumonia (PGAP). The latter two types are regarded as special forms, because they cannot be easily diagnosed and are still underdiagnosed and recognized almost locally in Japan.

DAB is characterized by a chronic inflammatory reaction on recurrent aspirated foreign particles in the bronchioles. Therefore, some of its risk factors, such as neurologic disorders, dementia, cardiovascular diseases, dysphagia, or being bedridden, should be carefully considered. Centrilobular nodular shadows with branching opacities on the chest computed tomography (CT) scan may efficiently diagnose diffuse bronchiolitis. Recurrent bronchorrhea, bronchospasm, or dyspnea episodes are also suggestive of DAB.

Repetitive episodes of productive cough or symptoms consistent with esophageal reflux while sleeping are common in PGAP. Patients with PGAP often develop pyrexia in the following morning. Chest radiographs, or CT scans show mild and/or multiple small infiltrates. Swallowing dysfunction characterized by prolonged latent time for the swallowing reflex may predispose patients with PGAP.

These types of aspiration pneumonia should be carefully considered in order to determine hidden risks of recurrent aspiration and to propose other aspects of management.

Keywords Diffuse aspiration bronchiolitis · Post-gastrectomy aspiration pneumonia · Swallowing disorder · Elderly

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1 Introduction

Aspiration pulmonary diseases can be classified into four categories: aspiration pneumonia, Mendelson's syndrome, diffuse aspiration bronchiolitis (DAB), and post-gastrectomy aspiration pneumonia (PGAP). DAB and PGAP are not considered to be acute onset due to chronic inflammation caused by recurrent aspiration. They are regarded as special forms of aspiration pneumonia, because they cannot be easily diagnosed. Unfortunately, they are still underdiagnosed and are recognized almost locally in Japan.

Here, the clinicopathological features of these unique types of aspiration pneumonia are discussed based on previous pivotal articles.

2 Diffuse Aspiration Bronchiolitis (DAB)

Diffuse bronchiolitis caused by aspiration of gastric contents or foreign particles is incidentally found during an autopsy in an elderly patient. The term diffuse aspiration bronchiolitis (DAB) was first defined by Fukuchi et al. in 1989 [1]. They reported that it is characterized by a chronic inflammatory reaction to recurrent aspirated foreign particles in the bronchioles. After their proposal, several cases had been reported. Finally, Matsuse et al. published a pivotal report that reviewed its clinical, radiologic, and histologic features to facilitate earlier diagnosis of DAB [2].

They performed a retrospective observational study, enrolling 3253 consecutive autopsy cases at the Tokyo Metropolitan Geriatric Hospital (TGH) and 1627 cases at the University of Tokyo Hospital (TUH). Aspiration pneumonia (APN) occurred in 6.7% of TGH cases and 1.0% of TUH cases. DAB was found in 0.6% and 0.7% of all autopsy cases from the TGH and TUH, respectively. The incidence of DAB cases in the total of 4880 autopsy cases was 0.64% ($n = 31$). Clinical information of patients with DAB ($n = 23$) was assessed and compared with that of randomly selected patients with APN ($n = 40$).

The onset of DAB was significantly more insidious than that of APN (acute onset: 8.7% vs. 32.5%, $p < 0.02$). Neurologic disorders, dementia, and cardiovascular diseases were common comorbid diseases in DAB. About 52.2% and 69.6% of patients with DAB had oropharyngeal dysphagia and were bedridden, respectively. Symptoms and physical findings of DAB are shown in Table 11.1. Patients with DAB showed a relatively low inflammatory response, that is, 45.5% of them were febrile, as compared to 60.5% of those with APN. Leukocytosis (>10,000/mm^3) was observed in 38.1% of patients with DAB, compared to 60.0% in patients with APN. Chest radiograph showed diffuse small nodular shadows and areas of hyperlucency. Consolidation shadow was relatively rare. The gross appearance of the cut surface in the lung showed diffusely scattered miliary yellowish nodules that resembled those of diffuse panbronchiolitis (DPB) (Fig. 11.1). Foreign bodies or related giant cells were found in the bronchioles in 89.5% of patients with DAB and 41.5%

Table 11.1 Presenting symptoms and clinical findings in patients with DAB [2]

	No. of patients (%)
Presenting symptoms	
Cough	14 (60.9)
Sputum	19 (82.6)
Dyspnea	10 (43.5)
Physical findings	
Crackles	10 (43.5)
Wheezes	10 (43.5)
Edema	4 (17.4)

Values are mean ± SD: body temperature, 37.2 ± 0.9 °C; pulse rate, 92.2 ± 19.0 min^{-1}; and respiratory rate, 26.3 ± 8.4 min^{-1}

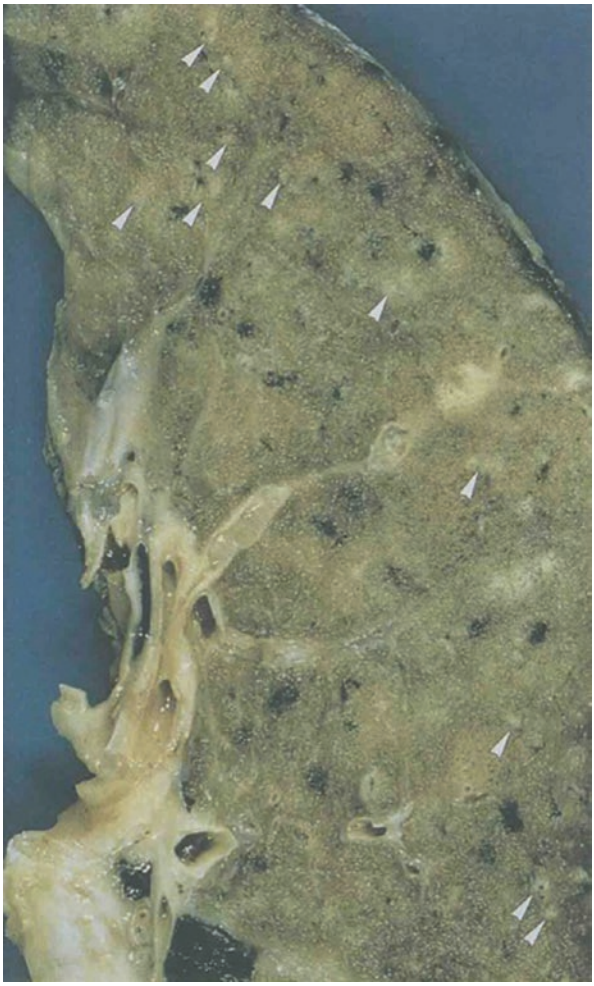

Fig. 11.1 Macroscopic view of the lung tissue with DAB [2]. A cut surface of autopsy lung obtained from a patient with DAB, showing many fine yellowish nodules (arrowheads) on the parenchyma, which resemble the DPB finding

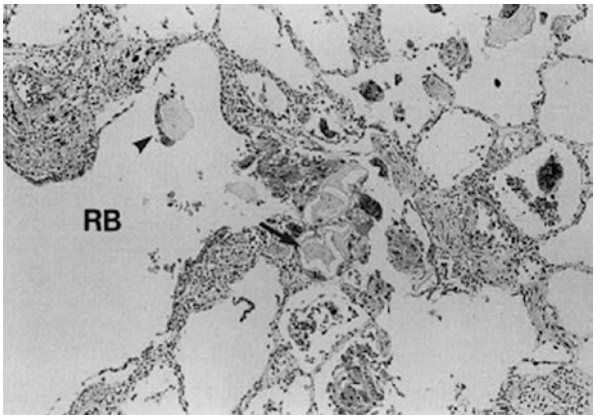

Fig. 11.2 Histologic view of DAB [2]. A longitudinal section of a bronchiole in DAB. There is lymphocytic infiltration in the respiratory bronchiole wall. The bronchiole lumen contains the foreign material (arrow) and foreign body giant cells (arrowhead). Other foreign materials are also noted in the alveolar ducts and alveolar sacs, with associated foreign body giant cells. RB = respiratory bronchiole (hematoxylin-eosin, original magnification ×200)

with APN, whereas the alveolar space was affected in 47.4% and 79.2% of patients with DAB and APN, respectively ($p < 0.01$) (Fig. 11.2).

They also demonstrated that DAB should be suspected in any elderly patient with recurrent episodes of bronchorrhea, bronchospasm, and dyspnea, especially when taking meals. DPB is often accompanied by sinusitis; however, DAB is not related with sinusitis. DAB may also often masquerade as late-onset asthma, because it is characterized by chronic recurrent infection, bronchospasm, and dyspnea. High index of suspicion is necessary to diagnose DAB. Bronchorrhea and bronchospasm related to oral intake, oropharyngeal dysphagia, and associated neurologic disorders are factors distinguishing DAB from DPB and late-onset asthma.

Diffuse bronchiolar disease due to chronic occult aspiration may also occur in relatively young individuals without symptoms suggesting recurrent aspiration. Barnes et al. reported four cases of diffuse bronchiolar disease with persistent cough and dyspnea and had been eventually diagnosed with surgical lung biopsy as giant cells containing aspirated foreign material [3]. Radiologic assessment efficiently distinguished diffuse bronchiolar from other diseases. Chest radiographs showed regional or disseminated nodular shadows and hyperlucency, whereas chest CT demonstrated diffuse centrilobular nodules and branching opacities, indicating bronchiolitis (Fig. 11.3).

Silent aspiration during sleep may demonstrate diffuse aspiration bronchiolitis in elderly people. Few studies reported that half of healthy volunteers may aspirate oropharyngeal contents during sleep [4, 5]. Considering that oropharyngeal disorders frequently occur in elderly people, DAB might be extremely common. Nevertheless, DAB is still considered to be rare.

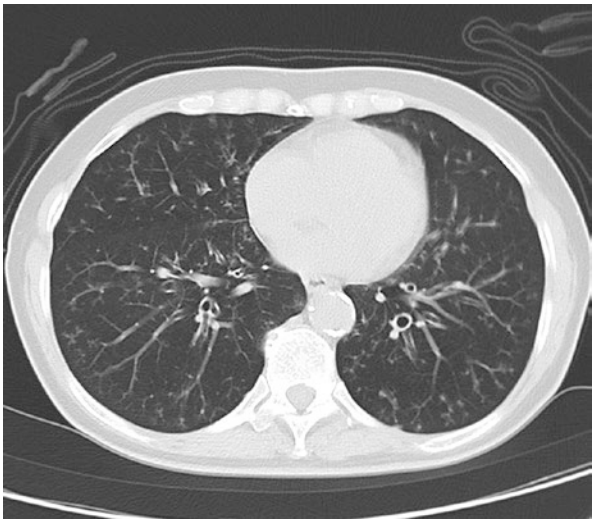

Fig. 11.3 Computed tomography scan of the chest showing a background of numerous centrilobular nodules and branching opacities in bilateral lungs [The author's own experience]

Interestingly, Barnes et al. reported that two of the four patients were obese (body mass index, 32.4 and 51.8), and three of them had been treated for gastroesophageal reflux disease (GERD) by proton pump inhibitors. Obesity is a risk factor of GERD. Kahrilas et al. demonstrated upper sphincter pressure in healthy people during sleep [6]. As sleep progresses, upper esophageal sphincter (UES) pressure declines from 40 ± 17 mmHg (awake) to 8 ± 3 mmHg (slow-wave sleep). They also observed that UES pressure increased transiently with each inspiration. The UES pressure markedly decreasing during sleep may significantly diminish the barrier to nocturnal regurgitation and potential aspiration. Aspirated gastric contents itself may cause bronchiole inflammation. Obstructive sleep apnea (OSA) is frequently observed in obese patients. Esophageal reflux content is easily aspirated through intrathoracic negative pressure produced by inspiration effort of obstructive apnea. GERD associated with obesity and OSA may contribute to recurrent aspiration of gastric content and form diffuse bronchiolitis. Are these factors associated with DAB? Unfortunately, in Matsuse et al.'s report, no data were presented on GERD, sleep disturbance, or obesity. The diagnosis of DAB in Matsuse et al. were based on autopsy findings, and cases of diffuse bronchiolar diseases in Barnes et al. were consolidated by the surgical lung biopsy. However, performing lung biopsy is extremely difficult; therefore, some risk factors of DAB, such as neurologic disorders, dementia, cardiovascular diseases, dysphagia, or being bedridden, should be considered. Radiological findings such as centrilobular nodular shadows with branching opacities on chest CT scan may be used as an important tool to diagnose diffuse bronchiolitis. Recurrent episodes of bronchorrhea, bronchospasm, or dyspnea are also suggestive of DAB. The important clinical question on DAB to be elucidated is whether it is associated with GERD, obesity, or OSA.

3 Post-gastrectomy Aspiration Pneumonia (PGAP)

The term post-gastrectomy aspiration pneumonia (PGAP) was used for the first time in 1995 in a retrospective observational study conducted by Marumo, Homma, and Fukuchi at a single center in Japan [7]. Their previous study indicated that recurrent lower respiratory tract inflammation (RTI) was a frequent complication of patients who underwent previous total gastrectomy. Marumo et al. enrolled 216 among 314 patients who underwent total gastrectomy and stable for >1 year after the hospital discharge at the Tokyo Metropolitan Police Hospital. A total of 30 patients were excluded due to death or deterioration of their condition, and 186 patients were used in the analysis. Sixty patients had early gastric cancer, 110 had advanced gastric cancer, and the other 16 had malignant lymphoma, leiomyosarcoma, reactive lymphoid hyperplasia, or peptic ulcer. They were divided into three groups. The n-RTI group that did not have any RTI symptom such as cough, sputum, and pyrexia included 125 patients (67 men, 58 women, mean age 51.8 ± 10.8 years). The s-RTI group experienced sporadic (less than once a year) RTI symptoms. This group included 45 patients (31 men, 14 women, mean age 56.6 ± 9.4 years). The r-RTI group who experienced recurrent RTI (more than twice a year) consisted of 16 patients (11 men, 5 women, and mean age 56.8 ± 7.5 years). They evaluated the clinical characteristics of patients in the r-RTI group by comparing them with the other groups. The clinical profiles such as age, preoperative pulmonary function, glucose tolerance, alcoholic or smoking history, operative procedure (ρ-loop Roux-en-Y reconstruction or not), splenectomy, post-operative diagnosis, post-operative chemotherapy, stomal stenosis, and symptoms related to esophageal reflux (aspiration or misdeglutition, sensation of reflux, dyspnea attack while sleeping) were analyzed. Symptoms related to gastroesophageal reflux were more common in the r-RTI group ($p < 0.01$). As previously mentioned, majority of patients with r-RTI had repetitive episodes of productive cough or symptoms consistent with esophageal reflux while sleeping. Pyrexia frequently occurs in the following morning. Majority of patients tended to complain of pyrexia than of respiratory discomfort. These pyrexic attacks occurred every few weeks or months in most patients; therefore, some patients with mild or relatively few symptoms had been associated with common colds, and other patients with moderate to severe symptoms had been assumed to have chronic, intractable pneumonia, or pulmonary tuberculosis. Even patients with pyrexia alone without cough or sputum were observed. Work-up were performed in the early stage to rule out fever of unknown cause or post-splenectomy syndrome. It was only later that the correct diagnosis of pneumonia was established using chest radiographs or CT scans. Radiographs showed mild and/or multiple small infiltrates in many patients. These lesions could be detected only with chest CT radiographs in some patients. Based on chest radiograph or CT scan findings, the preferential distribution of pneumonia was not noted (the upper right lobe in 6 of 12 patients, right middle lobe 7, right lower lobe 4, left upper lobe 3, left upper lobe 4, and left low lobe 4). In this report, r-RTI indicative of PGAP is common but can easily escape the attention of clinicians due to atypical clinical manifestations. Patients with episodes of productive cough or symptoms

Table 11.2 Common characteristics of patients with r-RTI ($n = 16$) [7]

Characteristics
Esophageal reflux is common
Pyrexic attack after esophageal reflux while asleep
Pyrexia is recurring and easily ameliorated
Occasional case of line pyrexia (without any cough or sputum)
Strong inflammatory response in laboratory data on acute exacerbation
Overt infiltrate is common on chest radiographs with occasional equivocal or multiple infiltrate (chest CT confirmation preferable)
Prolonged latency in swallowing provocation test

similar with esophageal reflux while sleeping or pyrexia in the following morning can develop PGAP. The characteristics of patients with r-RTI are summarized in Table 11.2.

Bacterial sputum culture revealed *Enterobacter cloacae*, *Klebsiella pneumoniae*, *Haemophilus parainfluenzae*, *Klebsiella oxytoca*, and *Staphylococcus aureus*. No anaerobic agent was cultivated. Esophagogastric contrast radiography showed easy reflux of radio-opaque material in the supine position ($n = 6$); however, no pulmonary aspiration was observed. An airway epithelial injury after the repetitive reflux during sleep may deteriorate the local defense mechanism and subsequent bacterial infection. They indicated that advising patients with r-RTI to change the body position during sleep into the slight head-up position (semi-Fowler position) may effectively prevent the occurrence of aspiration after gastrectomy based on the result of small r-RTI samples. The swallowing provocation test indicated prolonged latency in all examined patients (3.62 ± 0.90 ms; $n = 5$) as compared with age-matched controls (1.79 ± 0.31 ms; $n = 14$) ($p < 0.001$). Swallowing dysfunction characterized by an elongated latent time for swallowing reflex predisposed patients to develop aspiration pneumonia. Therefore, prolonged latent time after gastrectomy may identify the causative relationship between gastrectomy and subsequent aspiration pneumonia. However, whether swallowing reflex can be altered after gastrectomy remains unclear.

Marumo et al. later reported that gastroesophageal reflux itself contributed to prolonged latent time of swallowing provocation [8]. They measured the latent time on the swallowing provocation test in patients with non-aspiration pneumonia (PN), post-gastrectomy aspiration pneumonia (PGAP), gastroesophageal reflux disease (GERD), and normal group (NR). The latent time was also prolonged in AP (2.83 ± 1.66 s, $p < 0.01$), PGAP (2.58 ± 1.40 s, $p < 0.05$), and GERD (2.40 ± 1.70 s, $p < 0.05$) as compared with NR (1.04 ± 0.56 s) but not in PN (1.46 ± 0.75 s). Protected specimen brushing was carried out to detect pathogenic organisms. Gram-negative rods (GNR) were detected in 20.0% of patients with PN, 53.3% with AP, and 76.5% with PGAP. The PGAP group showed a significantly higher rate of GNR ($p = 0.008$). These results suggest that GER may play an important role in the aspiration pulmonary disease as a disturbing factor of swallowing function.

Pellegrini et al. conducted a study to evaluate the incidence of aspiration in 100 patients in whom abnormal gastroesophageal reflux was objectively demonstrated

by a 24-h pH monitoring of the distal esophagus [9]. They found that 48% of patients were suspected to be aspirating gastroesophageal contents into the tracheobronchial tree. They divided them into four groups. Patients in the "aspirators group" aspirated refluxed gastric acid based on the complaint of sudden taste of acid in the mouth and throat, followed by cough or wheezing during or immediately after a reflux episode. They demonstrated repetitive pneumonia, prolonged acid exposure time, and elevated cricopharyngeal pressure. They also demonstrated esophageal motor abnormalities that interfered with the esophagus' ability to clear refluxed acid. Non-peristaltic contractions could propel refluxed contents into the pharynx, making aspiration a more likely event. However, non-aspirators also demonstrated prolonged acid exposure. Gastrectomy without anti-reflux procedure may reduce the distal esophageal segment pressure and result in easy reflux of gastrointestinal content followed by PGAP, even if it does not contain gastric juice with lower pH. In fact, Pellegrini et al. also reported that an anti-reflux procedure increased the distal esophageal pressure and reduced the esophageal acid exposure time to reflux episodes.

Miki et al. conducted a single-center prospective phase II trial [10], consisting of 85 patients aged ≥75 years histologically diagnosed with gastric adenocarcinoma, with ECOG performance status (PS) of 0–1, without previous chemotherapy or radiotherapy and with normal organ function, were recruited. The primary endpoint of this study was the incidence of post-operative pneumonia within 90 days post-operatively. Secondary end-points were post-operative length of hospital stay, post-operative complications, and rates of abnormal results on the screening test of swallowing dysfunction. Neck muscle stretching and simple respiratory training with the incentive spirometry were performed for all enrolled patients. The following exercise of suprahyoid upper esophageal sphincter opening muscles was performed: they sat and placed a hand on their forehead, pushed their head forward against the backward pressure of their hand for 5 s, and then repeated five times of the same movement for 1 s each. This set of exercise was performed three to five times a day. Symptom questionnaire, repetitive saliva swallowing test, and modified water swallow test were performed for this screening. If any of the screening tests was positive, they were referred to the rehabilitation medicine division and underwent videofluorographic swallowing study (VFSS). If VFSS results were abnormal, the rehabilitation team prepared an intensive individualized rehabilitation treatment program for all patients. All patients underwent the oral care program prepared by the dental team during the perioperative period. Three patients were diagnosed with post-operative pneumonia within 90 days post-operatively. The incidence of post-operative pneumonia was 3.5% (60% confidence interval [CI], 1.8–6.3%), and the upper limit of the CI was lower than the prescribed threshold rate of 7.8%. Screening for deglutition was positive in 26.7% of patients but post-operative pneumonia was not observed in these patients. This study implied that intensive approach for patients aged ≥75 years and positive of preoperative screening test by the team consisting of surgeons, rehabilitation medicine physicians, dentists, nurses, physical therapists, and speech-hearing-language therapists can prevent aspiration pneumonia after gastrectomy.

The important clinical questions that should be elucidated are as follows: (1) Is there any difference in the swallowing function and incidence of aspiration

pneumonia between patients with aspiration pneumonia who experienced gastrectomy and those who did not? (2) Can team approach based on the screening for swallowing disorder or geriatric intervention according to geriatric assessments lower the incidence of PGAP of elderly patients?

4 Conclusion

This study confirmed that there are special forms of aspiration pneumonia due to aging and gastrectomy. Therefore, these types of aspiration pneumonia should be considered to determine hidden risks of recurrent aspiration and to propose other aspects of care. The exact pathophysiology of these disorders remains to be elucidated, in order to derive the appropriate management.

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References

1. Fukuchi Y, Matsuse T, Kida K. Infection- clinico-pathological profile of diffuse aspiration bronchiolitis (DAB). Nihon Kyobu Shikkan Gakkai Zasshi. 1989;27(5):571–7.
2. Matsuse T, Oka T, Kida K, Fukuchi Y. Importance of diffuse aspiration bronchiolitis caused by chronic occult aspiration in the elderly. Chest. 1996;110(5):1289–93. https://doi.org/10.1378/chest.110.5.1289.
3. Barnes TW, Vassallo R, Tazelaar HD, Hartman TE, Ryu JH. Diffuse bronchiolar disease due to chronic occult aspiration. Mayo Clin Proc. 2006;81(2):172–6. https://doi.org/10.4065/81.2.172.
4. Gleeson K, Eggli DF, Maxwell SL. Quantitative aspiration during sleep in normal subjects. Chest. 1997;111(5):1266–72. https://doi.org/10.1378/chest.111.5.1266.
5. Huxley EJ, Viroslav J, Gray WR, Pierce AK. Pharyngeal aspiration in normal adults and patients with depressed consciousness. Am J Med. 1978;64(4):564–8. https://doi.org/10.1016/0002-9343(78)90574-0.
6. Kahrilas PJ, Dodds WJ, Dent J, Haeberle B, Hogan WJ, Arndorfer RC. Effect of sleep, spontaneous gastroesophageal reflux, and a meal on upper esophageal sphincter pressure in normal human volunteers. Gastroenterology. 1987;92(2):466–71. https://doi.org/10.1016/0016-5085(87)90143-0.
7. Marumo K, Homma S, Fukuchi Y. Postgastrectomy aspiration pneumonia. Chest. 1995;107(2):453–6. https://doi.org/10.1378/chest.107.2.453.
8. Marumo K, Homma S. Role of gastro-esophageal reflux (GER) and swallowing latency in aspiration pulmonary diseases. Nihon Kokyuki Gakkai Zasshi. 2005;43(6):333–9.
9. Pellegrini CA, DeMeester TR, Johnson LF, Skinner DB. Gastroesophageal reflux and pulmonary aspiration: incidence, functional abnormality, and results of surgical therapy. Surgery. 1979;86(1):110–9.
10. Miki Y, Makuuchi R, Honda S, Tokunaga M, Tanizawa Y, Bando E, et al. Prospective phase II study evaluating the efficacy of swallow ability screening tests and pneumonia prevention using a team approach for elderly patients with gastric cancer. Gastric Cancer. 2018;21(2):353–9. https://doi.org/10.1007/s10120-017-0736-3.

Chapter 12
Significant Roles of the Simple Two-Step Swallowing Provocation Test (STS-SPT) in Aspiration Pneumonia but Not in Food Swallowing Problems: Does the STS-SPT Have a Special Role for Detecting Silent Aspiration?

Shinji Teramoto

Abstract We have developed a simple two-step swallowing provocation test (STS-SPT) for detection of swallowing disorder in patients with a risk of aspiration pneumonia (AP). The test was utilized for the water-stimulated swallowing reflex at suprapharynx in humans. Because the two-step simulation of different volume of water identified the high or low risk of aspiration during night; STS-SPT can predict high risk of pathological aspiration at the bedside. The sensitivity and specificity of first-step SPT using 0.4 mL of water for the detection of aspiration pneumonia were 100% and 83.8%, respectively. Those of the second-step SPT using 2.0 mL of water were 76.4% and 100%, respectively. Because the STS-SPT can be performed without any need for special patient effort or cooperation, it should be effective in diagnosing AP in a wide variety of patients, including those who are bedridden. Although STS-SPT is not the definitive test for detecting the risk of aspiration pneumonia, it is a promising test simply to exclude patients at low risk for aspiration. However, patients at high risk may still require videofluoroscopy to guide an appropriate therapy.

The test is also applied for decision of safe feeding, procedure of nasogastric tube replacement, prediction of COPD exacerbation, and sleep apnea associated aspiration problems.

Keywords Silent aspiration · Screening test · Simple swallowing provocation test · Safe feeding · Supine position · Post-stroke pneumonia

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1 Introduction: Clinical Significance of Silent Aspiration in Elderly Pneumonia

Pneumonia is a leading cause of death in most developed countries including Japan [1]. Aspiration pneumonia is an intuitive clinical phenotype familiar to clinicians and is the dominant form of pneumonia in an ageing population [2–4]. A previous study indicated that approximately 60% of hospitalised patients with community-acquired pneumonia (CAP) should be diagnosed as aspiration pneumonia [3]. Recent studies have resulted that aspiration pneumonia increases with age and with residence in a nursing home [5, 6]. Although aspiration pneumonia is dominant in nursing and healthcare-associated pneumonia (NHCAP), research on AP has been limited, because of the lack of a universal definition for AP [7, 8].

Sir William Osler said 100 years ago that pneumonia is a friend of the aged. Elderly people are considerably more liable to suffer from pneumonia, in particular aspiration pneumonia, and often die [9]. That is why the predictive factors for aspiration pneumonia should be determined in the high-risk subgroup of elderly people with nursing care.

Recent studies revealed that silent aspiration during night is a most important risk and/or cause of AP [10–18]. Unfortunately, the silent aspiration cannot be detected by conventional swallowing function testing, since silent aspiration occurs during night [17, 18].

For this purpose, we have developed a new type of swallowing function tests, such as simple two-step swallowing provocation test (STS-SPT). We show the method and applicability of STS-SPT in this chapter.

2 The STS-SPT and Its Clinical Application

2.1 What Is the Simple Two-Step Swallowing Provocation Test (STS-SPT)?

Swallowing function needs to be evaluated when diagnosing aspiration pneumonia, and various methods are available for this purpose, including the water swallowing test [15, 19, 20], repetitive saliva swallowing test [21], swallowing provocation test (Fig. 12.1) [22], and videofluoroscopic examination of swallowing [23–25] (Table 12.1). All of these methods are useful in the diagnosis of swallowing disorders, but tests to diagnose aspiration pneumonia differ from tests to detect ingestion and swallowing disorders. Videofluoroscopic ingestion and swallowing disorders are performed with the patient in a sitting position and are not directly related to aspiration pneumonia. Swallowing disorder tests that enable evaluation of the risk of silent aspiration during the night or when the patient is unaware are important in the diagnosis of aspiration pneumonia. Special tests to evaluate ingestion and swallowing function, such as videoendoscopic and/or videofluoroscopic examination of

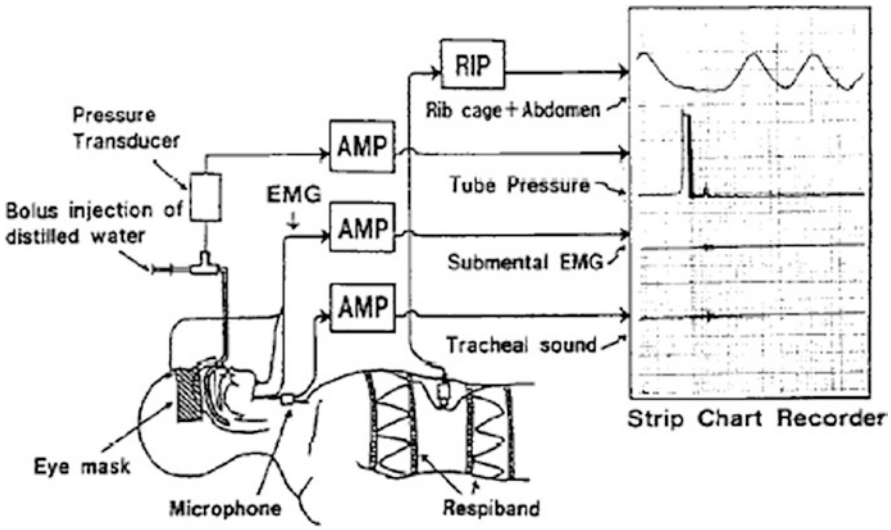

Fig. 12.1 How to perform the RSST. The patient is instructed to swallow their own saliva as many times as possible in 30 s. The examiner counts the number of swallows completed successfully by palpating the laryngeal movement. Commonly, when the examiner is sitting across from the patient, respiration is monitored by residents. The swallowing reflex is induced by injecting a bolus of 0.4–2 mL of distilled water into the suprapharynx through a 5 Fr small nasal catheter (internal diameter, 0.5 mm) while the subjects were laying at supine position. The timing of bolus injection of water is monitored by pressure transducer. Swallowing reflex is monitored using genioglossus muscles movement by EMG. The measurements are recoded on strip chart recorder

Table 12.1 Tests to evaluate swallowing function

1. Screening method
Bedside swallowing function evaluation Clinical examination, (dysphonia, dysarthria, abnormal gag reflex, abnormal volitional cough, Cough after swallow, and voice change after swallow) Changes in arterial oxygen saturation when swallowing at bedside Repeated repetitive saliva swallowing test (RSST) Water swallowing test
2. More detailed assessment of swallowing function
Confirmation of uptake into lungs of radioisotopes applied to teeth Swallowing provocation test Simple two-step swallowing provocation test (STS-SPT) Videofluoroscopy (videofluoroscopic swallow study (VSS), Videoendoscopy (fiberoptic endoscopic evaluation of swallowing (FEES)) Water swallowing test Radioisotope aspiration technique

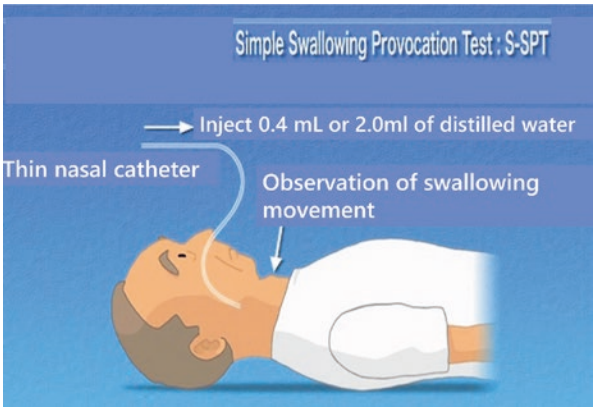

Fig. 12.2 Swallowing provocation test. The swallowing reflex was induced by injecting a bolus of 0.4 mL (first step) and 2 mL (second step) of distilled water into the suprapharynx through a 5 Fr small nasal catheter (internal diameter, 0.5 mm) while the subjects were laying at supine position. The appropriate placement of catheter tip at suprapharynx was identified visually. Laryngeal movement, used to indicate swallowing, was observed visually. Subjects were unaware of the timing of the actual injection. The injection was administered near the end of expiration. A volume of water was injected in 1–2-s bursts, to keep the velocity of injection similar between trials. The swallowing reflex was evaluated by the latency of the response, that is, the time (LT) from the water injection to the onset of swallowing. The response time was measured with a stopwatch

swallowing, are unrelated to the prediction of pneumonia, and no evidence for the utility of these tests has been reported.

Although most of the swallowing function tests were performed on upright position, the simple swallowing provocation test (Fig. 12.2) is conducted with patients in a supine position [16, 17]. This practical test is very simple, informative, and can be done at the bedside. The equipment is very limited, only thin nasal catheter and distilled water are necessary.

This simple and easy access test offers superior sensitivity and specificity in detecting swallowing disorders that lead to pneumonia [18]. In terms of simplicity, the water swallowing test is also useful [18, 26]. It has also reported that an impairment of the pharyngeal phase of swallowing, first-step SPT reliably detects aspiration risk in acute stroke patients. However, in patients with a sole or predominant impairment of the oral phase of swallowing and a relatively intact pharyngeal phase, fiberoptic endoscopic evaluation of swallowing (FEES), or additional clinical features rather than SPT more specifically indicating oral-phase pathology should be considered to accurately judge the patient's aspiration risk [18].

Regardless of form, if a patient can swallow water well, swallowing function is thought to be relatively maintained. Conversely, patients who cannot swallow water well are considered to display a swallowing disorder, providing grounds for a diagnosis of aspiration pneumonia.

2.2 Protocol of Simple Two-Step Swallowing Provocation Test (STS-SPT)

The swallowing reflex was induced by injecting a bolus of 0.4 mL (first step) and 2 mL (second step) of distilled water into the suprapharynx through a 5 Fr small nasal catheter (internal diameter, 0.5 mm) while the subjects were laying at supine position [15, 16]. The appropriate placement of catheter tip at suprapharynx was identified visually. Laryngeal movement, used to indicate swallowing, was observed visually [27]. Subjects were unaware of the timing of the actual injection. The injection was administered near the end of expiration. A volume of water was injected in 1–2-s bursts, to keep the velocity of injection similar between trials. The swallowing reflex was evaluated by the latency of the response, that is, the time (LT) from the water injection to the onset of swallowing. The response time was measured with a stopwatch. In our experience, the mean value of LT in normal volunteers is 1.7 ± 0.7 s [29]. SPT was classified as normal when the LT was less than 3 s [28, 29].

3 Predictive Roles of STS-SPT in Aspiration Pneumonia

3.1 STS-SPT Detects the Risk of Aspiration Pneumonia

The water-stimulated swallowing reflex using STS-SPT is considerably impaired in patients with aspiration pneumonia when compared with the responses to swallowing provocation in control subjects without aspiration pneumonia. A greater volume of water was necessary to induce the swallowing reflex in patients with aspiration pneumonia than in the control subjects. In the controls, 0.4 mL of water was sufficient to elicit swallowing; however, 2 mL was insufficient to initiate swallowing in some patients with aspiration pneumonia. The greater threshold of swallowing induction by water may influence dysphagia in patients with aspiration pneumonia.

A normal response to the first-step SPT indicates a low risk of aspiration pneumonia and that the abnormal response to the second-step SPT identifies persons with a high risk of aspiration pneumonia. The sensitivity and specificity of first-step SPT for the detection of aspiration pneumonia were 100% and 83.8%, respectively. Those of the second-step SPT were 76.4% and 100%, respectively. Although SPT is not the definitive test for detecting the risk of aspiration pneumonia, the current study provides a screening test simply to exclude patients at low risk for aspiration. Patients at high risk may still require videofluoroscopy to guide an appropriate therapy (Table 12.1).

Because the STS-SPT can be performed without any need for special patient effort or cooperation, it should be effective in diagnosing AP in a wide variety of patients, including those who are bedridden.

3.2 A Comparison of Predictive Roles of STS-SPT in Aspiration Pneumonia with that of Water Swallowing Test

We performed two-step WST (WST) on subjects who performed STS-SPT [15]. Subjects were asked to drink 10 mL (first step) and 30 mL (second step) of distilled water from a cup within 10 s while in a sitting position. Subjects who drank the water without interruption, cough, or wet-hoarse voice were considered normal. Subjects who drank the water but with evidence of aspiration or who could not drink the water within 10 s were considered abnormal.

As a result, the sensitivity and specificity of first-step WST for detecting aspiration pneumonia were 71.4% and 70.8%, respectively; those for the second-step were 72% and 70.3%, respectively. It has been reported that the sensitivity and specificity of WST to recognize aspiration, as detected by the videofluoroscopic examination, were 76% and 59%, respectively [19]. Although a WST is useful in detecting the swallowing disorder in older subjects and patients with stroke [19, 20], its sensitivity and specificity for detecting aspiration pneumonia were lower than those of SPT.

4 Roles of STS-SPT on Safe Feeding After Stroke

We have developed a simple two-step swallowing provocation test (STS-SPT) for detection of swallowing disorder in stroke patients with aspiration pneumonia. STS-SPT can identify at the bedside, stroke patients with high risk of pathological aspiration [30–33].

We also prospectively assessed the relation between the responses to STS-SPT and the development of aspiration pneumonia in patients with acute stroke. Twenty patients with acute stroke, mean age 70 years (SD 4) were included. We did an S-SPT on all patients. Three the lowest volume of water eliciting the swallowing reflex within 3 s of water injection was taken to be the threshold volume. Based on the clinical assessments, stepwise food intake was generally started 2 weeks after the stroke. We investigated the frequency of aspiration pneumonia after the stroke for 3 months. Seven patients were diagnosed as having aspiration pneumonia, with evidence of an inflammatory response on chest radiography in a dependent pulmonary segment, with an increased white blood cell count. The other 13 patients had no evidence of aspiration pneumonia for 3 months. Patients without aspiration pneumonia had threshold volumes for swallowing reflex of less than 1.2 mL 3 weeks after onset of stroke and those with aspiration pneumonia showed no swallowing response to 2.0 mL of water or had a higher threshold for the swallowing reflex at 4 weeks after onset of stroke.

Our results suggest that patients with the threshold volume of less than 1.0 mL of water may regain swallowing function after the stroke and protect laryngeal

penetration. Patients with threshold volumes for swallowing reflex higher than 2.0 mL are at high risk of the development of aspiration pneumonia. The timing of starting the food intake should be delayed in patients with high threshold volumes of swallowing. STS-SPT is, therefore, useful to estimate the timing of feeding after stroke and may be clinically important for safe feeding.

5 Roles of STS-SPT on Placing Nasogastric Tubes in Stroke Patients

The STS-SPT method is applied for the different situation of post-stroke patients. The placing nasogastric tubes (NGT) is often difficult in stroke patients. The placing technique using STS-SPT is an alternate approach for the patients.

A thin catheter was inserted through the nostril with its tip being placed in the oropharynx [29]. The NGT was placed through the other nostril in approximately the same position. The swallowing reflex was induced by bolus injection of 0.5–2.0 mL of distilled water through the thin catheter. At the onset of swallowing, which was identified by observation of the characteristic upward laryngeal movement, the NGT was moved forward. This method is effective to place NGT in right place for the patients. The placing of NGT by inducing the swallowing reflex is a useful alternative if the conventional method fails. It has been reported that the method is successful in 14 of 16 patients (87.5%) in whom the conventional approach repeatedly resulted in tracheal positioning of the tube or its coiling in the mouth. Inoue et al. also reported that a success rate of NGT was 82.6% in elderly patients with stroke (mean age 86.7 years). This procedure also suggested that less distressing for the patients, leading to a significantly smaller increase in heart rate and systolic blood pressure, as compared with the conventional methods. This seems to be the fact that with this method significantly fewer attempts were needed until correct placement of the tube was achieved.

6 Predictive Roles of STS-SPT in COPD Exacerbation

It has been recognized that dysphagia is an important risk of chronic obstructive pulmonary disease (COPD) exacerbation. To detect the risk for COPD exacerbation, early identification of dysphagia is necessary to identify the future risk of execration and its prognosis in the patients. Because STS-SPT effectively detects the swallowing reflex abnormality in COPD, the utilization of STS-SPT may contribute to decrease the frequency of COPD exacerbation, resulting in the better prognosis of the CODP patients.

7 Roles of STS-SPT in Dysphagia in Sleep Apnea Patients

The swallowing reflex is well coordinated with breathing patterns in normal humans. However, patients with obstructive sleep apnea syndrome (OSAS) may have a swallowing disorder that reflects the abnormal function of nerves and muscles in the suprapharynx. The swallowing function in the subject was tested using a swallowing provocation test. The swallowing reflex was determined according to the following criteria: latent time (LT), the time following a bolus injection of distilled water at the suprapharynx to the onset of swallowing; inspiratory suppression time (IST), the time from the termination of swallowing to the next onset of inspiration; and threshold volume, the minimum volume of water (range, 0.4–2 mL) that could evoke the swallowing response. Whereas the LT values in patients with OSAS were larger than the LT values in the control subjects, the IST values (which may reflect the switching mechanism from deglutition apnea to breathing) were actually shorter. In addition, a greater bolus volume was necessary to elicit swallowing in patients with OSAS than was necessary in the control subjects. Therefore, patients with OSAS are likely to exhibit an impaired swallowing reflex, probably due to the perturbed neural and muscular function of the upper airways. It has been reported that elderly patients with OSAS have higher risk of aspiration pneumonia, probably due to impaired swallowing reflex and aspiration.

8 Conclusion

The STS-SPT is a convenient and highly reproducible method to screen the aspiration risk in patients with a risk of aspiration pneumonia at the bedside.

References

1. Manabe T, Teramoto S, Tamiya N, Okochi J, Hizawa N. Risk factors for aspiration pneumonia in older adults. PLoS One. 2015;10(10):e0140060. https://doi.org/10.1371/journal.pone.0140060.
2. Koivula I, Sten M, Mäkelä PH. Risk factors for pneumonia in the elderly. Am J Med. 1994;96(4):313–20.
3. Teramoto S, Fukuchi Y, Sasaki H, Sato K, Sekizawa K, Matsuse T, Japanese Study Group on Aspiration Pulmonary Disease. High incidence of aspiration pneumonia in community- and hospital-acquired pneumonia in hospitalized patients: a multicenter, prospective study in Japan. J Am Geriatr Soc. 2008;56(3):577–9.
4. Marik PE, Kaplan D. Aspiration pneumonia and dysphagia in the elderly. Chest. 2003;124(1):328–36.
5. Marrie TJ. Epidemiology of community-acquired pneumonia in the elderly. Semin Respir Infect. 1990;5(4):260–8.
6. Muder RR. Pneumonia in residents of long-term care facilities: epidemiology, etiology, management, and prevention. Am J Med. 1998;105(4):319–30.

7. Fukuyama H, Yamashiro S, Tamaki H, Kishaba T. A prospective comparison of nursing- and healthcare-associated pneumonia (NHCAP) with community-acquired pneumonia (CAP). J Infect Chemother. 2013;19(4):719–26.
8. Lanspa MJ, Jones BE, Brown SM, Dean NC. Mortality, morbidity, and disease severity of patients with aspiration pneumonia. J Hosp Med. 2013;8(2):83–90.
9. Osler W. The principles and practice of medicine. New York: D. Appleton and Co.; 1998. p. 109.
10. Teramoto S. Novel preventive and therapeutic strategy for post-stroke pneumonia. Post-stroke pneumonia. Expert Rev Neurother. 2009;9:1187–200.
11. Teramoto S. Clinical significance of aspiration pneumonia and diffuse aspiration bronchiolitis in the elderly. J Gerontol Geriat Res. 2014;3:142. https://doi.org/10.4172/2167-7182.1000142.
12. Matsuse T, Oka T, Kida K, Fukuchi Y. Importance of diffuse aspiration bronchiolitis caused by chronic occult aspiration in the elderly. Chest. 1996;110:1289–93.
13. Matsuse T, Teramoto S, Matsui H, Ouchi Y, Fukuchi Y. Widespread occurrence of diffuse aspiration bronchiolitis in patients with dysphagia, irrespective of age. Chest. 1998;114:350–1.
14. Teramoto S, Ishii T, Yamamoto H, et al. Significance of chronic cough as a defence mechanism or a symptom in elderly patients with aspiration and aspiration pneumonia. Eur Respir J. 2005;25:210–1.
15. Teramoto S, Fukuchi Y. Detection of aspiration and swallowing disorder in older stroke patients: simple swallowing provocation test versus water swallowing test. Arch Phys Med Rehabil. 2000;81(11):1517–9.
16. Teramoto S, Matsuse T, Fukuchi Y, Ouchi Y. Simple two-step swallowing provocation test for elderly patients with aspiration pneumonia. Lancet. 1999;353(9160):1243.
17. Kikuchi R, Watabe N, Konno T, Mishina N, Sekizawa K, Sasaki H. High incidence of silent aspiration in elderly patients with community-acquired pneumonia. Am J Respir Crit Care Med. 1994;150(1):251–3.
18. Arai T, Yasuda Y, Takaya T, Ito Y, Hayakawa K, Toshima S, Shibuya C, Suematsu F, Shibayama M, Yoshimi N, Kashiki Y. Technetium tin colloid test detecting symptomless dysphagia and ACE inhibitor prevented occurrence of aspiration pneumonia. Int J Mol Med. 2000 Jun;5(6):609–10.
19. DePippo K, Holas MA, Reding MJ. Validation of the 3-oz water swallow test for aspiration following stroke. Arch Neurol. 1992;49:1259–61.
20. Feinberg MJ. Radiographic techniques and interpretation of abnormal swallowing in adult and elderly patients. Dysphagia. 1993;8:356–8.
21. Tamura F, Mizukami M, Ayano R, Mukai Y. Analysis of feeding function and jaw stability in bedridden elderly. Dysphagia. 2002;17:235–41.
22. Teramoto S, Sudo E, Matsuse T, Ohga E, Ishii T, Ouchi Y, Fukuchi Y. Impaired swallowing reflex in patients with obstructive sleep apnea syndrome. Chest. 1999;116:17–21.
23. Splaingard M, Hutchins B, Sulton L, Chaudhuri G. Aspiration in rehabilitation patients: videofluoroscopy vs. bedside clinical assessment. Arch Phys Med Rehabil. 1988;69:637–40.
24. Logemann JA. Role of modified barium swallow in management of patients with dysphagia. Otolaryngol Head Neck Surg. 1997;116:335–8.
25. Johnson ER, McKenzie SW, Sievers A. Aspiration pneumonia in stroke. Arch Phys Med Rehabil. 1993;74(9):973–6.
26. Teramoto S, Matsuse T. Two-step swallowing provocation test for elderly patients. Lancet. 1999;353(9171):2246.
27. Warnecke T, Teismann I, Meimann W, Olenberg S, Zimmermann J, Krämer C, Ringelstein EB, Schäbitz WR, Dziewas R. Assessment of aspiration risk in acute ischaemic stroke - evaluation of the simple swallowing provocation test. J Neurol Neurosurg Psychiatry. 2008 Mar;79(3):312–4.
28. Marumo K, Homma S, Fukuchi Y. Postgastrectomy aspiration pneumonia. Chest. 1995 Feb;107(2):453–6.
29. Teramoto S, Matsuse T, Matsui H, Ohga E, Saitoh E, Ishii T, Tomita T, et al. The simple swallowing provocation test as a means of screening for swallowing disorders: a comparison with the water swallowing test. J Jpn Respir Soc. 37(6):466–70.

30. Teramoto S, Matsuse T, Fukuchi Y. Decision-making for safe feeding after stroke [letter]. Lancet. 2000;356:1352.
31. Dziewas RL, Demann P, Konrad C, et al. Simple method for placing nasogastric tubes in patients with dysphagia. Lancet. 2001;358:725.
32. Dziewas R, Schilling M, Konrad C, Stögbauer F, Lüdemann P. Placing nasogastric tubes in stroke patients with dysphagia: efficiency and tolerability of the reflex placement. J Neurol Neurosurg Psychiatry. 2003;74:1429–31.
33. Inoue K, Takano H, Yamada T, et al. Nasogastric tubes in patients with dysphagia. Lancet. 2002;359:81.

Chapter 13
Predictive Roles of the Repetitive Saliva Swallowing Test (RSST) in Aspiration Pneumonia and Other Respiratory Diseases: Does the RSST Have a Predictive Role in Aspiration Pneumonia and Other Respiratory Diseases?

Yuki Yoshimatsu

Abstract Patients with dysphagia do not always present with subjective symptoms. However, asymptomatic dysphagia can also cause clinical issues, especially in those with respiratory conditions. Therefore, adequate screening is an essential beginning to their care. The repetitive saliva swallowing test (RSST) is one of the safest screening methods for dysphagia; it can be easily performed by nonprofessionals in any setting. There is evidence of its predictive values in aspiration pneumonia, chronic obstructive pulmonary disease (COPD), artificial ventilation, and other conditions. Additionaly, it has recently been found to be a strong predictor of the risk of future COPD exacerbation. The cost-effectiveness, harmlessness, and simplicity make it an optimal screening method for the large population of patients with respiratory conditions, although different cutoff values may be useful in different populations. It also takes into account multiple aspects of the swallowing ability, such as respiration, musculature, cognition, and general well-being.

Keywords Aspiration · Screening · Repetitive saliva swallowing test · RSST · COPD

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1 Introduction: Dysphagia Screening

Patients with dysphagia do not always present with subjective symptoms. Therefore, adequate screening is an essential beginning to the total care of aspiration pneumonia. A screening test is performed to identify patients at risk of dysphagia and to evaluate the necessity for a more comprehensive evaluation. These screenings are performed in a wide range of patients, by a wide range of professions. Therefore, it must be a simple and safe method, while assuring a high sensitivity to the specific patient group intended to be screened.

There are many screening tests for dysphagia and aspiration (Table 13.1). Screening tests can range from self-assessed questionnaires, such as the Eating Assessment Tool (EAT-10) [1] and Sydney Swallow Questionnaire (SSQ) [2], to observer-rated questionnaires and diagnostic procedures performed by an examiner such as the repetitive saliva swallowing test (RSST) [3], water swallow test (WST) [4], modified water swallow test (mWST) [5], and food test [6]. Examination techniques such as pulse oximetry [7] and cervical auscultation [8] can be used by itself or in conjunction with other screening tests. The simple swallow provocation test (SSPT) [9] is a unique method that allows screening for the pharyngeal sensation and does not require patient cooperation. There are also tests that allow for screening in patients with a tracheal cannula, such as Evan's blue dye test [10] and modified Evan's blue dye test (MEBDT) [11].

Clinicians must select the appropriate screening method depending on the setting, patient group, capacity, and evidence. Among these tests (and numerous others), the repetitive saliva swallowing test (RSST) is one of the safest methods. Originally being developed to screen for dysphagia, it has been applied to other purposes in recent years. In this chapter, we will investigate the RSST and the physiology underlying its broad applicability in respiratory disorders.

2 The RSST and Its Utility

2.1 What Is the RSST?

The RSST was developed in Japan by Oguchi et al. to safely and simply screen patients for functional dysphagia [3]. When performing this test, the patient is instructed to swallow their own saliva as many times as possible in 30 seconds. The examiner counts the number of swallows completed successfully by palpating the patient's laryngeal movement. Commonly, the index finger and middle finger are placed on the hyoid and thyroid cartilage (Fig. 13.1). In their original report, the authors suggest that when the RSST value is less than three times per 30 seconds, further investigation for functional dysphagia should be planned.

Table 13.1 Screening tests for dysphagia

No.	Name of test	Method	Criteria	Significance
1	Eating Assessment Tool (EAT-10) [1]	A 10-item questionnaire of subjective symptoms of dysphagia	≥ 3 points suggest alterations in swallow	Identify patients with dysphagia who should undergo further assessment.
2	Sydney Swallow Questionnaire (SSQ) [2]	17-item self-reported questionnaire of subjective symptoms of dysphagia using a visual analogue scale	The higher the score obtained, the higher the swallowing dysfunction (no cutoff value)	Measures symptomatic severity of dysphagia. Useful in assessing the response to a treatment
3	Repetitive saliva swallowing test (RSST) [3]	Repeat dry swallows for 30 seconds	< 3 is recommended for further assessment	Low cost and harm. Evidence in relation to aspiration, pneumonia, and COPD exacerbation
4	Water swallow test (WST) [4]	Swallow 30 mL of water	Drinking all within 5 seconds without choking is considered normal	Evaluates oral and pharyngeal phages of swallowing
5	Modified water swallow test (mWST) [5]	Swallow 3 mL of cold water	Check for choking, multiple swallows, or inability to swallow	Safer than the water swallow test
6	Food test [6]	Swallow 4 g of pudding placed on the tongue	Check for choking, changes in breathing or voice, or inability to swallow	For some patients, more acceptable than the WST
7	Pulse oximetry [7]	Measure oxygen saturation while eating/drinking	A decrease of ≧ 2–5 % is abnormal (but is not solely dependent on aspiration). Further assessment is recommended	Cutoff not validated. Increased utility when combined with WST
8	Cervical auscultation [8]	Auscultate above the cricoid cartilage in front of the sternocleidomastoid muscle during swallow	Listen for abnormal sounds of swallowing and swallowing-related respiration	Applicable in any setting but accuracy is questionable
9	Simple swallow provocation test (SSPT) [9]	Apply water (0.4 mL, 2.0 mL) through a nasal cannula placed in the oropharynx, and measure time to swallow initiation	≥ 3 seconds is abnormal	Does not require patient cognition. Can screen for oropharyngeal sensation
10	Evan's blue dye test [10]	In patients with a tracheal cannula, place food dye in the oral cavity	Abnormal if food dye is aspirated from the cannula	Can be performed at the bedside without patient cooperation. Accuracy is questionable
11	Modified Evan's blue dye test (MEBDT) [11]	In patients with a tracheal cannula, try oral intake with food dye	Abnormal if dye is aspirated from the cannula	Can test different consistencies (solids, thickened liquids, etc.). Accuracy is questionable

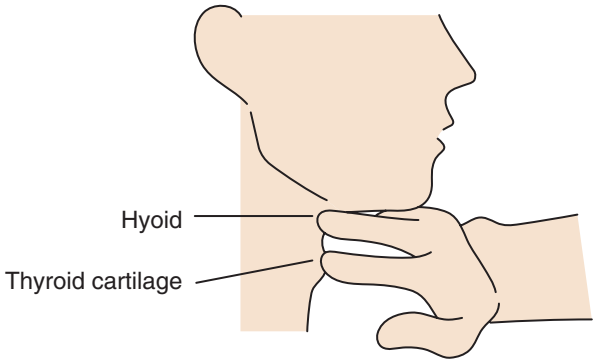

Fig. 13.1 How to perform the RSST. The patient is instructed to swallow their own saliva as many times as possible in 30 seconds. The examiner counts the number of swallows completed successfully by palpating the laryngeal movement. Commonly, when the examiner is sitting across from the patient, the middle finger of the examiner is placed on the patient's hyoid and the index finger on the thyroid cartilage. If the examiner is standing next to the seated patient, the examiner may place their index finger on the hyoid and the middle finger on the thyroid cartilage (illustration by Yurika Hirano)

2.2 The Cutoff Value of RSST

The cutoff value of the RSST was derived from the original study on 60 healthy participants [3]. Its validity has been further established through their next study of 131 patients with functional dysphagia (the cause being cerebrovascular disorder in 94 patients, brain tumor 6, brain injury 6, other neurological diseases 13, pneumonia 8, and other 4) [12]. An RSST score less than three was statistically significantly related to aspiration on videofluoroscopy, and the sensitivity and specificity were 0.98 and 0.66, respectively. The high sensitivity of RSST supports its effectiveness as a screening method for dysphagia.

2.3 Comparison of RSST to Other Screening Methods

Factors that may affect the ability to perform RSST include not only pharyngeal movement but also oral function, salivation, muscular structure and strength, holding and restarting the respiratory cycle repeatedly (the coordination of respiration and deglutition), cognition, and cooperation. It is not the best measure to screen for one specific part of the swallowing function (i.e., the simple swallow provocation test is a better method to screen for pharyngeal sensorial declination). On the contrary, it may be said that the RSST is an optimal method to screen for the whole swallowing ability. Its necessity to repeat actual swallows enables one to differentiate between those who can swallow (but possibly only in slow or uncoordinated reactions) and those who can repeatedly swallow as a means of safe oral intake.

As shown in Table 13.1, various screening methods of dysphagia have been developed. Compared to the other commonly performed tests, the RSST requires only a watch to measure 30 seconds. There is no need for specific equipment, hence

causing no economic burden. There is no associated risk of aspiration with the test, and it only requires one minute, including the time to explain the procedure. The feasibility of the RSST makes it an excellent screening tool for all settings, including any outpatient clinic, primary care setting, and even home care or nursing facilities, as long as the patient is alert and able to cooperate.

Another notable characteristic of the RSST is its safety. As it only solely requires the patients themselves to perform a purely physiological function (a dry swallow), there is no known risk associated with the test. There need not be any concern about complications that may be associated with other screening methods such as nasal membrane damage, aspiration, choking, or pneumonia. This encourages all professions and even family members to perform this test. Another important factor to consider when performing a screening test is the risk of transmitting droplets (aerosols) during the test. Most swallowing assessments involve this risk, including examination of the oral mechanism, testing cough reflexes, as well as the WST, mWST, food test, SSPT, Evan's blue dye test, and MEBDT. Because the RSST holds no risk of transmitting aerosols, it is a safe test from the standpoint of infection control. During the worldwide pandemic of the novel coronavirus, the RSST was the only test that the Society of Swallowing and Dysphagia of Japan permitted in regions that the infection had spread.

3 Predictive Roles of RSST in Aspiration Pneumonia

Over the years, some studies have used the RSST for more than the initial aim, which was to screen for the necessity for dysphagia assessment. In these further studies, the RSST has sometimes been modified to establish its efficacy in screening similar conditions, while the cutoff level has also been modified from its original level.

3.1 Treatment of Aspiration Pneumonia

For example, in a prospective observational study regarding the switch from intravenous to oral antimicrobials in 38 aspiration pneumonia patients, one of the criteria was RSST $\geq$2 [13]. In an analysis of feeding function and jaw stability in bedridden elderly patients, RSST $\leq$3 was considered abnormal [14].

3.2 Oral Intake in Aspiration Pneumonia

The RSST has also been investigated as one of the measures to predict the ability of oral food intake. In a study of 77 elderly patients admitted for acute pneumonia who were fasting due to aspiration risk, RSST $\geq$1 was found to be 1 of the predictors of oral intake at discharge (AUC 0.77, sensitivity 0.81, specificity 0.67) [15]. In this study, the Glasgow Coma Scale had a higher AUC (0.79) with a sensitivity and specificity of 0.71 and 0.80. There was no predictive effect in the modified water swallow test, simple swallowing provocation test, or cough test.

4 Predictive Roles of RSST in COPD

4.1 Dysphagia in COPD

Chronic obstructive pulmonary disease (COPD) is considered to be a systemic disease, and dysphagia is increasingly recognized as one of its common complications. Dysphagia is found to be related to a higher risk of COPD exacerbation and, hence, mortality. Therefore, early identification of dysphagia is essential in this group. In order to efficiently identify dysphagia in patients with COPD, it is necessary to understand the pathophysiology of why this group of patients develops dysphagia.

Patients with COPD have many factors that can cause dysphagia [16]. These include patient background factors, such as a smoking history and older age; respiratory issues, such as altered respiratory patterns and a lack of respiration-swallowing coordination; and systemic complications of COPD, such as GERD, sarcopenia, frailty, and sleep apnea syndrome. These multifactorial causes of dysphagia make dysphagia in patients with COPD unique. Therefore, when screening for dysphagia in patients with COPD, a method that is capable of screening for multiple aspects of the swallowing function is necessary.

4.2 Dysphagia Screening in COPD

The simple swallow provocation test (SSPT) has been reported to be a predictor of COPD exacerbation [17, 18]. However, this is not as simple as it sounds, both for physicians as well as patients. It requires the preparation of specific supplies and abundant practice and also causes discomfort for the patients. One previous study stated the possibility that the RSST may be a better method than the SSPT to detect dysphagia in patients with mild COPD [19].

4.3 RSST in COPD

Recently we reported the usefulness of RSST in detecting patients at high risk of COPD exacerbation. In our previous retrospective study, the results of the RSST were significantly lower in patients with exacerbations in the previous year [20]. In the prospective study following this, patients with a low RSST were at significantly higher risk of exacerbation in the next year (Fig. 13.2) [21]. The RSST was a stronger predictor of COPD exacerbation than the presence of exacerbation in the past year (which is currently considered as the strongest predictor). Additionally, the optimal cutoff value of the RSST in this population was found to be 5. Patients with COPD who scored 5 or more in RSST were at significantly lower risk of having an

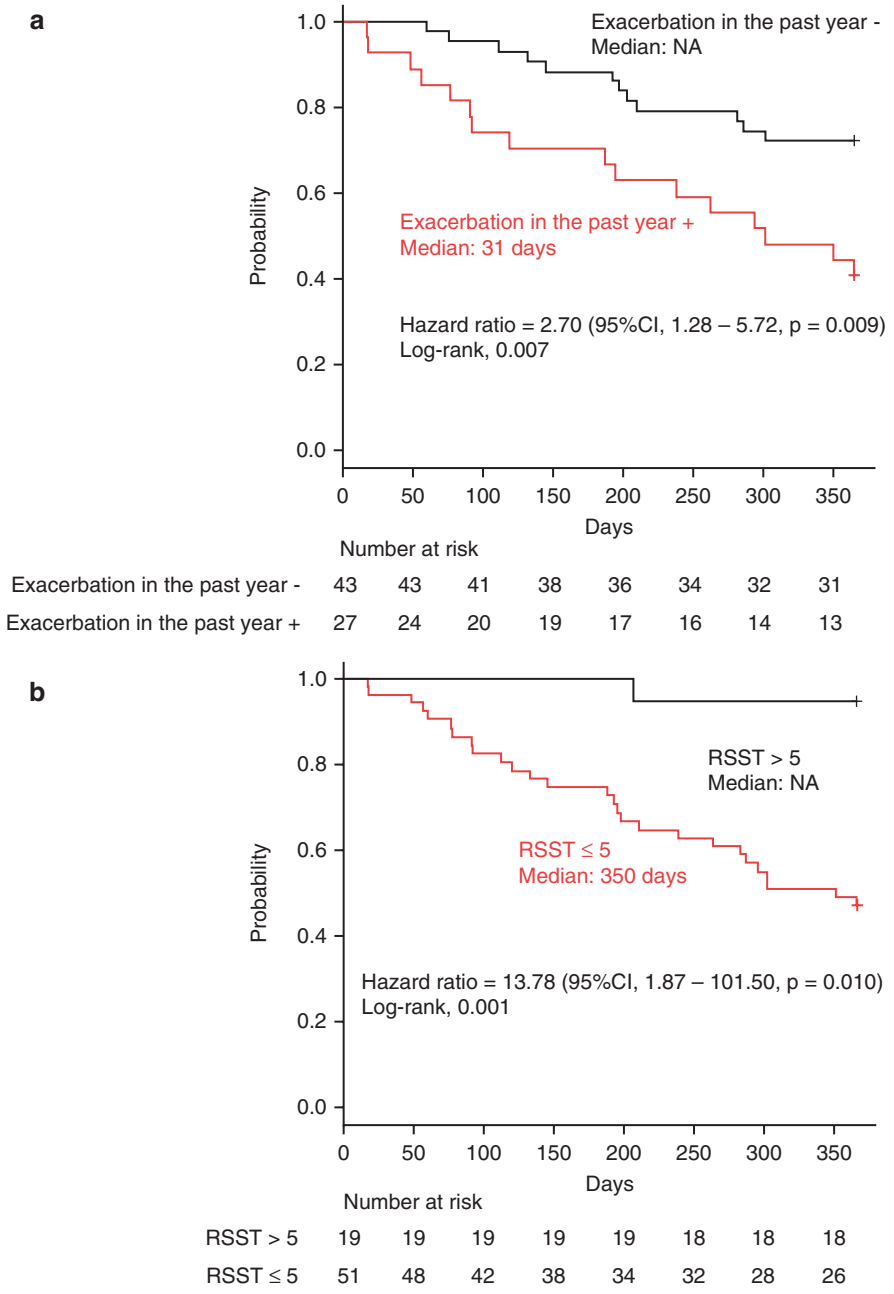

Fig. 13.2 Kaplan-Meier curves of the time to first exacerbation (any severity) (**a**) stratified by the presence of exacerbation in the past year and (**b**) stratified by the RSST cutoff value of 5. The time to first exacerbation was significantly longer in patients with no history of exacerbation in the past year than in those with exacerbation (**a**) and in those with an RSST value >5 (**b**). The RSST was a stronger predictor of exacerbation than a history of exacerbation [21]

exacerbation in the following year. Moreover, no patients who scored 5 or more had a moderate or severe exacerbation in the following year. The RSST may therefore be useful in screening for those at risk of exacerbation, especially moderate to severe exacerbation.

4.4 Why Is the RSST a Good Predictor in COPD?

Reportedly, the altered respiratory pattern due to COPD contributes to the increase in the incidence of inspiration occurring immediately before or after swallowing, as opposed to the more common pattern in which expiration occurs before and after swallowing in healthy individuals. The incoordination between respiration and swallowing is said to put patients with COPD at risk of aspiration [22], along with other systemic factors discussed before. We suspect that this is why screening tests such as the EAT-10, SSPT, and WST, which concentrate on a specific aspect of swallowing, are not particularly useful in this population. The RSST, which requires sufficient respiration-swallowing coordination, adequate musculature, cognition, and general well-being, is an effective method of screening for the swallowing function as a whole. RSST may also be more convenient in subclinical (asymptomatic) dysphagia, which is common in patients with mild COPD.

4.5 Swallowing During Artificial Ventilation

In a study of healthy volunteers, the occurrence rate of inspiration after swallow was found to be higher during bi-level positive airway pressure (BiPAP) than in normal breathing and continuous positive airway pressure (CPAP). When inspiration (instead of expiration) happens after swallowing, it is considered to be a risk factor of aspiration. In this study, RSST was a predictive variable of the risk of an inspiration to occur after swallow [23]. As artificial ventilation is often used for respiratory support during COPD exacerbations, this is an interesting area for further research.

5 Variables Affecting the RSST

When performing the RSST in the clinic, examiners are frequently confronted with patients insisting that they were not able to perform the RSST well because of xerostomia. We can assure them not to worry, as this has been already investigated.

5.1 Saliva Secretion

Whether saliva secretion or mouth dryness affects the results of the RSST is still controversial. In a study of 120 non-patients and 40 patients with dysphagia, neither the actual amount of saliva secretion nor the subjective dryness of the mouth affected the RSST results significantly [24]. It has been reported that there is little relation between xerostomia, or the feeling of dryness in the mouth, and actual hyposalivation [25]. However, it is true that some studies show the relation between dry mouth and a lower RSST value [26].

5.2 Effect of Moisturizing the Mouth Before the RSST

Whether the use of artificial saliva enables more swallows than without it has been investigated by Oguchi et al. in their original report [1]. According to this study, moisturizing the mouth with artificial saliva showed no significant change in the results of the RSST. On the other hand, lemon water has been reported to increase saliva secretion. It reduced the elongation of swallowing intervals (thus increasing the RSST score) with the effect depending on the concentration of lemon water [27]. However, as feasibility is one of the strengths of RSST over other screening tests, the usage of lemon water may not be applied easily. Therefore, it is currently recommended that the RSST be done without the use of water, but minimal amounts of water (such as 1 mL) may be used to moisturize the mouth if necessary. If patients attempt to accumulate saliva in their oral cavity prior to the RSST in order to score higher in the test, they should be instructed not to do so.

5.3 Patient Background

In the previously stated study, the number of doctor-prescribed medications did not affect the RSST results [24]. This study did, however, find that the swallowing frequency in RSST was less in older subjects than younger, and in female subjects than their male counterparts. Implementing a different cutoff depending on age and gender groups may be a topic to be considered for investigation.

5.4 Cognitive Function

Cognitive function and verbal communication ability are vital in performing the RSST successfully. In a study of elderly patients, RSST could only be completed by 59%, the inability mostly being due to dementia [28]. Prior to the test, clinicians

should make sure the patient understands that their maximal effort is required during the test.

5.5 Examiner

The sensitivity and specificity of RSST for aspiration differ among studies [12, 26]. The study population has a considerable influence on this difference. Although it is a relatively simple test, the understanding and experience of the examiner may also affect the results [26]. Therefore, when performing this test with others, it is essential to practice and share how to count the number of swallows correctly. Some patients have more subtle thyroid cartilage or hyoid movement than others. Also, patients often attempt to swallow but do not complete the swallow (i.e., the swallow is interrupted). To correctly count the number of swallows during the RSST, it is helpful first to ask the patient to swallow once to become familiar with that particular patient's swallow pattern on palpation.

6 Conclusion

The RSST is a convenient, safe, and reliable method to screen the swallowing function in multiple aspects. It has a predictive role in aspiration pneumonia and COPD exacerbation. Its high feasibility and sensitivity make it an optimal screening tool.

References

1. Belafsky PC, Mouadeb DA, Rees CJ, Pryor JC, Postma GN, Allen J, et al. Validity and reliability of the eating assessment tool (EAT-10). Ann Otol Rhinol Laryngol. 2008;117(12):919–24.
2. Wallace KL, Middleton S, Cook IJ. Development and validation of a self-report symptom inventory to assess the severity of oral-pharyngeal dysphagia. Gastroenterology. 2000;118:678–87.
3. Oguchi K, Saitoh E, Mizuno M, Baba M, Okui M. Suzuki M (2000) the repetitive saliva swallowing test (RSST) as a screening test of functional dysphagia (1). Normal values of RSST. Jpn J Rehabil Med. 2000;37:375–82.
4. Kubota T, Mishima H, Hanada M, Namba I, Kojima Y. Dysphagia paralytica in cerebrovascular disease: screening test and its clinical application. Sogo Rihabiriteshon. 1982;10:271–6. [in Japanese]
5. Osawa A, Maeshima S, Tanahashi N. Water-swallowing test: screening for aspiration in stroke patients. Cerebrovasc Dis. 2013;35:276–81.
6. Tohara H, Saitoh E, Mays KA, Kuhlemeier K, Palmer JB. Three tests for predicting aspiration without videofluorography. Dysphagia. 2003;18:126–34.
7. Higo R, Tayama N, Watanabe T, Nito T. Pulse oximetry monitoring for the evaluation of swallowing function. Eur Arch Otorhinolaryngol. 2003;260:124–7.
8. Bergström L, Svensson P, Hartelius L. Cervical auscultation as an adjunct to the clinical swallow examination: a comparison with fibre-optic endoscopic evaluation of swallowing. Int J Speech Lang Pathol. 2014;16:517–28.

9. Teramoto S, Fukuchi Y. Detection of aspiration and swallowing disorder in older stroke patients: simple swallowing provocation test versus water swallowing test. Arch Phys Med Rehabil. 2000;81:1517–9.
10. Garuti G, Reverberi C, Briganti A, Massobrio M, Lombardi F, Lusuardi M. Swallowing disorders in tracheostomised patients: a multidisciplinary/multiprofessional approach in decannulation protocols. Multidiscip Respir Med. 2014;9:36.
11. Bechet S, Hill F, Gillheaney O, Walshe M. Diagnostic accuracy of the modified Evan's blue dye test in detecting aspiration in patients with tracheostomy: a systematic review of the evidence. Dysphagia. 2016;31:721–9.
12. Oguchi K, Saitoh E, Mizuno M, Baba M, Okui M, Suzuki M. The repetitive saliva swallowing test (RSST) as a screening test of functional dysphagia (2). Validity of RSST. Jpn J Rehabil Med. 2000;38:383–8.
13. Uni M, Nishimura N, Yamano Y, Ishikawa G, Kitamura A, Tomishima Y, Jinta T, Takahashi O, Deshpande G, Chohnabayashi N. Efficacy of early switch from intravenous to oral antimicrobials in patients with aspiration pneumonia: a prospective observational study. Respir Investig. 2015;53:225–31.
14. Tamura F, Mizukami M, Ayano R, Mukai Y. Analysis of feeding function and jaw stability in bedridden elderly. Dysphagia. 2002;17:235–41.
15. Oba S, Tohara H, Nakane A, Tomita M, Minakuchi S, Uematsu H. Screening tests for predicting the prognosis of oral intake in elderly patients with acute pneumonia. Odontology. 2017;105:96–102.
16. Steidl E, Ribeiro CS, Gonçalves BF, Fernandes N, Antunes V, Mancopes R. Relationship between dysphagia and exacerbations in chronic obstructive pulmonary disease: a literature review. Int Arch Otorhinolaryngol. 2015;19:74–9.
17. Terada K, Muro S, Ohara T, et al. Abnormal swallowing reflex and COPD exacerbations. Chest. 2010;137:326–32.
18. Kobayashi S, Kubo H, Yanai M. Impairment of the swallowing reflex in exacerbations of COPD. Thorax. 2007;62:1017.
19. Ohta K, Murata K, Takahashi T, Minatani S, Sako S, Kanada Y. Evaluation of swallowing function by two screening tests in primary COPD. Eur Respir J. 2009;34:280–1.
20. Yoshimatsu Y, Tobino K, Sueyasu T, et al. Repetitive saliva swallowing test and water swallowing test may identify a COPD phenotype at high risk of exacerbation. Clin Respir J. 2019;13:321–7.
21. Yoshimatsu Y, Tobino K, Sueyasu T, et al. Repetitive saliva swallowing test predicts COPD exacerbation. Int J Chron Obstruct Pulmon Dis. 2019;14:2777–85.
22. Nagami S, Oku Y, Yagi N, et al. Breathing-swallowing discoordination is associated with frequent exacerbations of COPD. BMJ Open Resp Res. 2017;4:e000202. https://doi.org/10.1136/bmjresp-2017-000202.
23. Hori R, Isaka M, Oonishi K, Yabe T, Oku Y. Coordination between respiration and swallowing during non-invasive positive pressure ventilation. Respirology. 2016;21:1062–7.
24. Persson E, Wårdh I, Östberg P. Repetitive saliva swallowing test: norms, clinical relevance and the impact of saliva secretion. Dysphagia. 2019;34:271–8.
25. Bagheri H, Damase-Michel C, Lapeyre-Mestre M, Cismondo S, O'Connell D, Senard JM, et al. A study of salivary secretion in Parkinson's disease. Clin Neuropharmacol. 1999;22(4):213–5.
26. Cheng YM, Lan SH, Hsieh YP, Lan SJ, Hsu SW. Evaluate five different diagnostic tests for dry mouth assessment in geriatric residents in long-term institutions in Taiwan. BMC Oral Health. 2019;19:106.
27. Haji T. The effect of lemon water on repetitive saliva swallowing, using intra-aural swallowing sound as an indicator. Jpn J Logop Phoniatr. 2017;58:135–42. (Article in Japanese)
28. Baba Y, Teramoto S, Hasegawa H, Machida A, Akishita M, Toba K. Characteristics and limitation of portable bedside swallowing test in elderly with dementia: comparison between the repetitive saliva swallowing test and the simple swallowing provocation test. Nihon Ronen Igakkai Zasshi. 2005;42:323–7. [Article in Japanese]

Chapter 14
Animal Models of Aspiration Pneumonia

Shinji Teramoto

Abstract Appropriate animal models of aspiration pneumonia may be required for studying the mechanism of aspiration and aspiration-induced pneumonia. Animal models of AP allow us to investigate distinct types of pneumonia at various disease stages, studies that are not possible in patients. AP animal models should have features of bacterial pneumonia and swallowing abnormality.

Our animal model of aspiration, using recombinant E1-deleted Ad vectors, may be advantageous relative to earlier models for assessing the development of aspiration pneumonia in association with disturbed upper airway reflexes, since DNA virus infection of bronchiolar epithelial cells in the lower respiratory tract can be assessed by the localization and intensity of LacZ gene expression The other candidate model of aspiration was applied for the experimental stroke in mice induced by occlusion of the middle cerebral artery. Aspiration pneumonia was caused by intranasal application of a small amount of *Streptococcus pneumoniae.*

Acid pneumonitis is a major cause of sterile acute lung injury (ALI), resulting in acute respiratory distress syndrome (ARDS) or Mendelson's syndrome. Several types of animal models of acid aspiration are available using a wide range of developed transgenic models.

Different types of animal models of both aspiration pneumonia and aspiration pneumonitis have considerably aided our understanding of disease pathogenesis and testing and developing of new treatment strategies.

Keywords Aspiration pneumonia · Aspiration pneumonitis · Animal models · Mendelson's syndrome · Acid aspiration · Acute lung injury (ALI)

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1 Introduction

Aspiration pneumonia (AP), which develops after the aspiration of oropharyngeal contents, differs from aspiration pneumonitis, wherein inhalation of gastric contents causes inflammation without the subsequent development of bacterial infection [1, 2]. Because the prognosis of AP as well as aspiration pneumonitis is poor in patients with advancing age, it is difficult to examine the novel therapeutic intervention inducing new drugs for the efficacy on their prognosis in older humans. Animal models of various types of pneumonia are increasingly being utilized in medical research and are responsible for accelerated progress in the treatment of pneumonia and drug development. Because the AP and aspiration pneumonitis are primarily caused by aspiration and swallowing disorder, their animal models should have features of dysphagia animal models in addition to models of respiratory tract injury and infection.

2 Need for Animal Models of AP and Aspiration Pneumonitis

Swallowing disorders and aspiration are often found in elderly subjects and patients with chronic pulmonary diseases [3–5]. Matsuse T and coworkers have demonstrated that recurrent silent aspiration causes a chronic inflammation of bronchioles accompanying a foreign body reaction in older humans [6]. Although many pulmonologists and geriatricians have recognized that silent aspiration and swallowing disorder might be very important for the pathogenesis of aspiration pneumonia and aspiration pneumonitis in older patients [7, 8], the precise mechanism of swallowing abnormality, the relative importance of the effect of age on dysphagia, and the effect of central depressants on aspiration have not been fully elucidated. In addition, suitable animal models for examination of the mechanism of both silent aspiration and massive aspiration such as Mendelson's syndrome have not been well established. Several investigators have shown that aspiration of radiolabeled oropharyngeal secretions into the lungs occurs in humans [5, 9, 10]. These studies suggested that oropharyngeal secretion aspirated to the lower airways during night but did not reveal the pathologic interaction between the aspirate content and airway epithelial infection processes. These studies revealed one aspect or one process in the development of aspiration pneumonia caused by swallowing disorder. Because silent aspiration does not always cause pneumonia, the study of aspiration or dysphagia alone does not provide sufficient information for examining the pathophysiologic mechanism of aspiration pneumonia.

On the other hand, animal models of aspiration pneumonitis have been widely studied. Acid pneumonitis spans the clinical spectrum from asymptomatic to acute respiratory distress syndrome (ARDS), characterized by neutrophilic alveolitis, and injury to both alveolar epithelium and vascular endothelium [11, 12]. Although

Table 14.1 Candidate biomarkers of gastric aspiration

Biomarkers	Summary of clinical data	Merit	Demerit
Pepsin in BAL fluid	Elevated in ICU population with subsequent pneumonia [14]	Easy to perform under intubated patients	Not easy to perfume under general condition Half-life of pepsin is short
Lipid-laden macrophage	Increase with gastric aspiration in a number of studies [15–17]	Semiquantitative	Nonspecific
Soluble-TREM-1	Single study reported higher levels in aspiration vs. non-aspirated patient groups [18]	Standardized measurement available for serum	Increased in trauma, infectious pneumonia [19, 20]
C-reactive protein (CRP)	Elevated in aspiration pneumonitis and pneumonia but cannot be used to distinguish them [21]	Easy to measure	Nonspecific
Procalcitonin (PCT)	Tested positive in aspiration patients vs. non-aspirated group [22] N-terminal procalcitonin elevated in aspiration patients [23]	Widely available	Much higher levels were observed in other infections

BAL bronchoalveolar lavage fluid, *Soluble-TREM-1* soluble-triggering receptor expressed on myeloid cells 1

human studies of ARDS patients have provided us with valuable information about the physiological and inflammatory changes in the lung caused by ARDS, it is difficult to determine the etiology of ARDS, and a wide range of pathophysiology have resulted in a lack of critical information that could be useful in developing therapeutic strategies. Numerous biomarkers have been studied in the context of aspiration-induced lung injury in humans and animals [13]. In Table 14.1, there are potential biomarkers for aspiration that have been studied in humans [12]. However, these markers are not enough to analyze the pathophysiology of aspiration lung disorders. Thus, animal models of aspiration pneumonitis have more advantages to examine the relationships between etiology and biomarkers in the lungs.

3 Animal Models of Aspiration Pneumonia (AP)

As we mentioned in the above sentences, appropriate animal models of aspiration pneumonia are useful to explore the mechanism of aspiration and aspiration-induced pneumonia. For the purpose of elucidating the role of disturbed upper airway reflexes in foreign body aspiration into lower airways, we administered an adenovirus (Ad) vector consisting of E1-deleted recombinant adenovirus carrying the *Escherichia coli* LacZ gene intranasally to mice or guinea pigs with or without

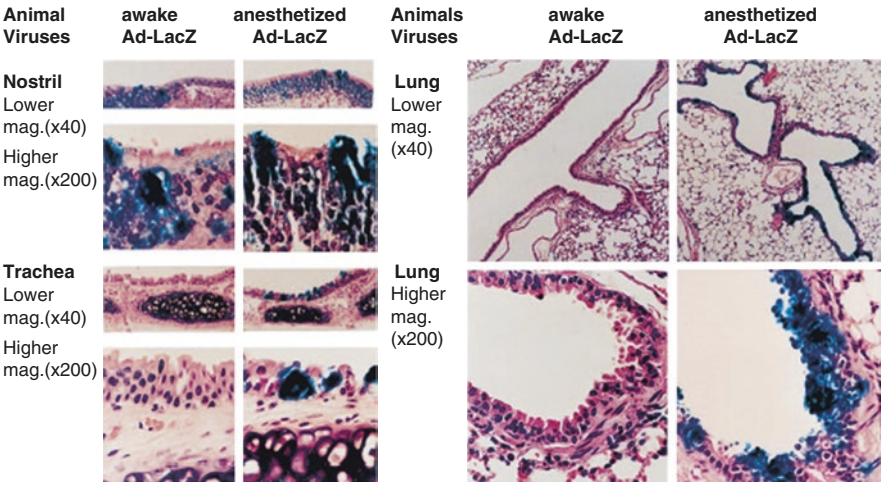

Fig. 14.1 Nostril and tracheal histology findings in 3-mo-old C57BL mice after intranasal administration of E1-deleted adenoviral vector (Ad-CMV-LacZ) with or without pentobarbital anesthesia. Awake mice were given PBS in place of pentobarbital sodium; anesthetized mice given pentobarbital sodium (5 mg/100 g body weight) intraperitoneally. Histologic sections were stained with X-gal and H&E. Original magnification: lower magnification, 340; higher magnification, 3200. Blue-stained cells were considered to express LacZ gene [25].

anesthesia [24, 25]. Because the Ad vector is known to infect airway cells and to express the *E. coli* LacZ gene in epithelial cells, the distribution in airways of intranasally administered solution containing Ad vectors can be identified by blue staining of LacZ with X-gal staining. In mice given Ad vector, but not phosphate-buffered saline (PBS), intranasally during anesthesia, there was LacZ gene expression in the nostrils, trachea, and lungs, suggesting that with X-gal staining, blue-stained cells indicated transferred LacZ gene expression (Fig. 14.1). These results suggested that aspiration of intranasal solution into lower airways was caused by disturbed upper airway reflexes during anesthesia. This process can be analyzed by the distribution of LacZ gene expression in airways. Further, these phenomena were observed in older animals even under light anesthetic condition, suggesting that aged animals are likely to aspirate oropharyngeal secretions during sedation and/or anesthesia. This novel model of aspiration, generated with the Ad-CMV-LacZ vector, may be useful for elucidating the mechanism of development of aspiration pneumonia in relation to age-related impairment of upper airway reflexes [24, 25].

Prass K et al. have reported the other candidate model of aspiration, which is applied for the experimental stroke in mice induced by occlusion of the middle cerebral artery (MCAO) [26]. Aspiration pneumonia was caused by intranasal application of a small amount of *Streptococcus pneumoniae* in phosphate-buffered saline 4 or 14 days after MCAO. Aspiration pneumonia in the stroke animals

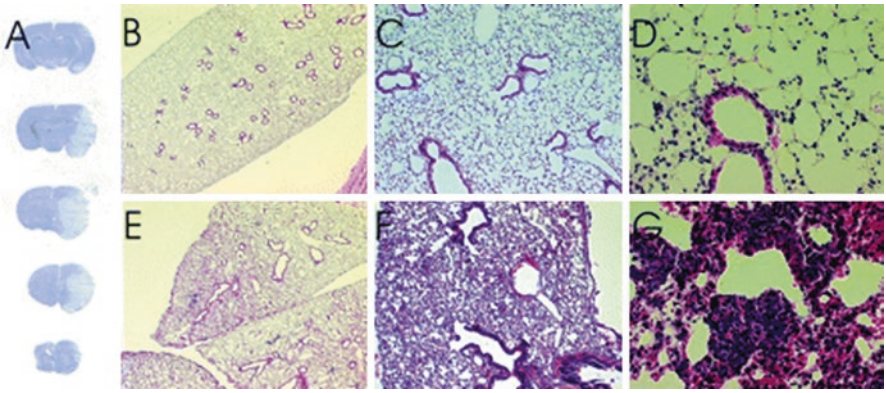

Fig. 14.2 Aspiration pneumonia in stroke but not in sham animals. (**a**) Histologic examination of the brain. Coronal sections of hematoxylin and eosin-stained mouse brain 72 hours after middle cerebral artery occlusion showing the infarction area. Lung histology of (**b**–**d**) sham and (**e**–**g**) stroke mice 18 hours after intranasal application of *S. pneumoniae*. Representative 12 μm sections of hematoxylin and eosin-stained lungs from (**e**–**g**) middle cerebral artery occlusion but not from (**b**–**d**) sham animals revealed signs of severe bacterial pneumonia characterized by (**e** and **f**) lobar consolidation, edema, necrosis, and neutrophilic infiltrates (**e** and **f**). Magnifications = (**b** and **e**) 25-fold, (C and F) 100-fold, or (**d** and **g**) 400-fold. Slides are representative of seven mice per group [26].

outlasted pathophysiologic state of acute stroke but was preventable by beta-adrenoreceptor blockade suggesting that immunodepression by sympathetic hyperactivity is essential for progression of bacterial aspiration to pneumonia (Fig. 14.2) [26]. It has been suggested that stroke-associated immunodepression increases the susceptibility to infection. However, it has also been reported that immunodepression following stroke may also have beneficial effects on the prognosis of stroke. Thus, before immunomodulatory therapy can be applied to stroke patients, we need to understand better the interaction of the brain and immune system after focal cerebral ischemia. In the experimental data, cilostazol, which is a phosphodiesterase III inhibitor, increases cAMP-responsive element binding protein (CREB) phosphorylation, leading to upregulation of several apoptotic gene and dopaminergic genes [27]. The CREB phosphorylation and increased expression of dopaminergic genes are involved in the improvement of swallowing function though in the increase of substance. Actually, in an animal model of ischemic stroke, cilostazol induced the increased levels of substance P and restores swallowing function in the animals [28]. Inversely, blockade of dopamine D1 receptors decreased substance P content in the laryngeal and pharyngeal mucosa, resulting in the impaired swallowing function in animals. Although extrapolation of these experimental results to the clinical situation must be performed with caution, the growing insight into these mechanisms may open new therapeutic avenues in the treatment of patients sustaining a stroke with aspiration pneumonia.

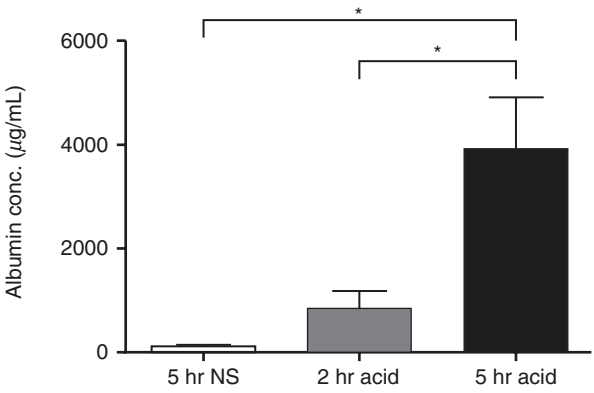

Fig. 14.3 Albumin leakage into airways following acid aspiration. Albumin concentration of cell-free BAL fluid from C57BL/6 mice at 2 hours and 5 hours post-acid aspiration. Acid aspiration was compared to 5 hours NS aspiration control ($n = 9$) using an unpaired t-test. Error bars indicate SEM. $* = p < 0.05$ [32].

3.1 Animal Models of Aspiration Pneumonitis

Acid pneumonitis is a major cause of sterile acute lung injury (ALI), resulting in ARDS, characterized by neutrophilic inflammation and alveolar epithelial injury in humans. This type of aspiration lung injury is categorized as chemical pneumonitis or aspiration pneumonitis [11]. Acid aspiration pneumonitis also induces extrapulmonary organ injury [29, 30]. The acidic component of the gastric aspiration contributes to both the pneumonitis and predilection to develop a secondary bacterial pneumonia. Aspiration pneumonia is also one of the leading risk factors for ALI and subsequent development of ARDS [12].

Translational animal models are valuable when their pathogenesis and pathophysiology accurately reproduce a concept proven in clinical settings. The murine acid aspiration model recreates a pathogenic scenario that reproduces the low pH pneumonitis injury in humans.

In our experiences, an animal model by administering hydrochloric acid (HCL) intratracheally to rats every 2 days for 2 weeks does not cause pneumonia [31]. There is no increase of lung free cells, TNFα production, and elastase-like activity in this animal model. However, Alluri R et al. reported that acid aspiration caused significant leakage of serum proteins into the airways in open tracheostomy gastric acid aspiration murine model. Albumin concentration in the BAL was increased following acid aspiration compared to normal saline (NS) controls at 2 hours and 5 hours (Fig. 14.3) [32]. They also reported that necrotic cells, loss of lung parenchymal architecture, cells and debris within airspaces, and significant polymorphonuclear leukocyte infiltration are observed in the animal model. Chiang SR et al. also found that 0.1 N acid aspirations alone directly induce lung injury but that the histopathological abnormal alterations of the lungs were not obvious in the mice. On the other hand, 0.1 N acid aspirations plus the inoculation of bacteria such as *Acinetobacter* into trachea caused considerable inflammation in the lungs of the same strain of mice [33]. Nagase et al. also reported that acute lung injury induced by acid aspiration of 2 mL/kg HCl (pH = 1.5) was slightly observed in control mice but severely observed in a disrupted cytosolic phospholipase A2 (cPLA2) gene [34]. The proteins

of cPLA2 gene may have a preventable role in acid aspiration-induced lung injury. Tavares A H et al. have recently reported that 2.5 mL/kg of intrabronchial HCl produced substantial yet sublethal acute lung injury in mice but lower doses of HCl did not result in reproducible and homogenous lung injury [35]. Thus, acid aspiration alone caused transient lung inflammation, but the injury is limited and recovered.

Aspiration of gastric contents induces not only severe pneumonitis but also large airway damages. This condition was determined as Mendelson's syndrome [36]. Mendelson's syndrome is chemical pneumonitis or aspiration pneumonitis caused by aspiration during anesthesia, especially during pregnancy. The condition is severe pneumonitis, but not bacterial pneumonia-like aspiration pneumonia. The lung can be injured directly, such as in pneumonia or with gastric acid aspiration, or indirectly [37]. The condition is closely related to acute respiratory distress syndrome (ARDS) [38]. It is important to develop and characterize an animal model of gastric acid aspiration. Maximal nonlethal lung injury in mice occurs after aspiration of 3.6 mL/kg of pH 1.25 HCl, which simulates gastric acid [39]. Gastric acid aspiration alters alveolar fluid clearance independent of pulmonary blood flow or vascular filtration [40]. Histologic characteristics of the gastric acid aspiration are an acute inflammatory alteration with patchy areas of neutrophilic inflammation, alveolar hemorrhage, and intra-alveolar and interstitial edema. The murine gastric acid aspiration model presented here using HCL employs an open tracheostomy and recreates a pathogenic scenario that reproduces the low pH pneumonitis injury in humans. Additionally, this model can be used to examine the interaction of a low pH insult with other pulmonary injurious entities including food particles and bacteria.

Chen Z et al. demonstrated that vagotomy decreases the neuronal activities of the medulla oblongata and alleviates neurogenic inflammation of airways induced by repeated intraesophageal instillation of HCl in guinea pigs [41]. This indicates that modulation of neuronal activities is a therapeutic option for neurogenic inflammation of airways following HCL exposure.

4 Conclusion

The risk of aspiration pneumonia increases in older adults, which is particularly relevant in the rapidly aging society of developed countries. Animal models of AP and aspiration pneumonitis are useful to examine the mechanism of aspiration-associated lung disorders in vivo. It is not easy to examine the acute therapeutic modality for AP and aspiration pneumonitis in humans. We have developed a novel animal model of aspiration and AP using recombinant E1-deleted Ad vectors under anesthesia. The other candidate model of aspiration was applied for the experimental stroke in mice induced by occlusion of the middle cerebral artery. As an animal model of aspiration pneumonitis, several types of animal models of acid aspiration are available using a wide range of developed transgenic models. We should further examine the mechanism of aspiration-associated lung disorders using a wide variety of animal models of AP and aspiration pneumonitis.

References

1. Niederman MS, Fein AM. Pneumonia in the elderly. Clin Geriatr Med. 1986;2:241–68.
2. Marrie TJ, Durant H, Yates L. Community-acquired pneumonia requiring hospitalization: 5-year prospective study. Rev Infect Dis. 1989;11:586–99.
3. Glesson K, Eggli DF, Maxwell SL. Quantitative aspiration during sleep in normal subjects. Chest. 1997;111:1266–72.
4. Feinberg MJ, Knebl J, Tully J, Segall L. Aspiration and the elderly. Dysphagia. 1990;5:1289–93.
5. Kikuchi R, Watabe N, Konno T, Mishina N, Sekizawa K, Sasaki H. High incidence of silent aspiration in elderly patients with community-acquired pneumonia. Am J Respir Crit Care Med. 1994;150:251–3.
6. Matsuse T, Oka T, Kida K, Fukuchi Y. Importance of diffuse aspiration bronchiolitis caused by chronic occult aspiration in the elderly. Chest. 1996;110:1289–93.
7. Nakagawa T, Sekizawa K, Arai H, Sasaki H. High incidence of pneumonia in elderly patients with basal ganglia infarction. Arch Intern Med. 1997;157(321–324):1997.
8. Harkness GA, Bentley DW, Roghmann KJ. Risk factors for nosocomial pneumonia in the elderly. Am J Med. 1990;89:457–63.
9. Huxley EJ, Viroslav J, Gray WR, Pierce AK. Pharyngeal aspiration in normal subjects and patients with depressed consciousness. Am J Med. 1978;64:564–86.
10. Brock-Utne JG, Winning TJ, Rubin J, Kingston HCG. Laryngeal incompetence during neurolept analgesia in combination with diazepam. Br J Anaeth. 1976;48:699–701.
11. Knight PR, Rutter T, Tait AR, Coleman E, Johnson K. Pathogenesis of gastric particulate lung injury: a comparison and interaction with acidic pneumonitis. Anesth Analg. 1993;77(4):754–60.
12. Raghavendran K, Nemzek J, Napolitano LM, Knight PR. Aspiration-induced lung injury. Crit Care Med. 2011;39(4):818–26.
13. Jaoude PA, Knight PR, Ohtake P, et al. Biomarkers in the diagnosis of aspiration syndromes. Expert Rev Mol Diagn. 2010;10(3):309–19.
14. Metheny NA, Clouse RE, Chang YH, et al. Tracheobronchial aspiration of gastric contents in critically ill tube-fed patients: frequency, outcomes, and risk factors. Crit Care Med. 2006;34(4):1007–15.
15. Ahrens P, Noll C, Kitz R, et al. Lipid-laden alveolar macrophages (LLAM): a useful marker of silent aspiration in children. Pediatr Pulmonol. 1999;28(2):83–8.
16. Corwin RW, Irwin RS. The lipid-laden alveolar macrophage as a marker of aspiration in parenchymal lung disease. Am Rev Respir Dis. 1985;132(3):576–81.
17. Parameswaran K, Anvari M, Efthimiadis A, et al. Lipid-laden macrophages in induced sputum are a marker of oropharyngeal reflux and possible gastric aspiration. Eur Respir J. 2000;16(6):1119–22.
18. El Solh AA, Akinnusi ME, Peter M, et al. Triggering receptors expressed on myeloid cells in pulmonary aspiration syndromes. Intensive Care Med. 2008;34(6):1012–9.
19. Mylotte JM, Goodnough S, Naughton BJ. Pneumonia versus aspiration pneumonitis in nursing home residents: diagnosis and management. J Am Geriatr Soc. 2003;51:17–23.
20. Giamarellos-Bourboulis EJ, Mouktaroudi M, Tsaganos T, et al. Evidence for the participation of soluble triggering receptor expressed on myeloid cells-1 in the systemic inflammatory response syndrome after multiple trauma. J Trauma. 2008;65(6):1385–90.
21. Gibot S, Cravoisy A. Soluble form of the triggering receptor expressed on myeloid cells-1 as a marker of microbial infection. Clin Med Res. 2004;2(3):181–7.
22. Pusch F, Wildling E, Freitag H, et al. Procalcitonin as a diagnostic marker in patients with aspiration after closed head injury. Wien Klin Wochenschr. 2001;113(17–18):676–80.
23. Nylen ES, Snider RH Jr, Thompson KA, et al. Pneumonitis-associated hyperprocalcitoninemia. Am J Med Sci. 1996;312(1):12–8.

24. Teramoto S, Matsui H, Ohga E, Ishii T, Matsuse T, Ouchi Y. A novel model of aspiration in young and old Guinea-pigs using LacZ gene transduction of adenovirus vector. Br J Anaesth. 1999;83(2):296–301.
25. Teramoto S, Matsuse T, Oka T, Ito H, Fukuchi Y, Ouchi Y. Investigation of effects of anesthesia and age on aspiration in mice through LacZ gene transfer by recombinant E1-deleted adenovirus vectors. Am J Respir Crit Care Med. 1998;158(6):1914–9.
26. Prass K, Braun JS, Dirnagl U, Meisel C, Meisel A. Stroke propagates bacterial aspiration to pneumonia in a model of cerebral ischemia. Stroke. 2006;37:2607–12.
27. Watanabe T, Zhang N, Liu M, Tanaka R, Mizuno Y, Urabe T. Cilostazol protects against brain white matter damage and cognitive impairment in a rat model of chronic cerebral hypoperfusion. Stroke. 2006;37:1539–45.
28. Zhang N, Miyamoto N, Tanaka R, Mochizuki H, Hattori N, Urabe T. Activation of tyrosine hydroxylase prevents pneumonia in a rat chronic cerebral hypoperfusion model. Neuroscience. 2009;158(2):665–72.
29. Weiser MR, Pechet TT, Williams JP, Ma M, Frenette PS, Moore FD, Kobzik L, Hines RO, Wagner DD, Carroll MC, Hechtman HB. Experimental murine acid aspiration injury is mediated by neutrophils and the alternative complement pathway. J Appl Physiol. 1997;83:1090–5.
30. Amigoni M, Bellani G, Scanziani M, Masson S, Bertoli E, Radaelli E, Patroniti N, Di Lelio A, Pesenti A, Latini R. Lung injury and recovery in a murine model of unilateral acid aspiration: functional, biochemical, and morphologic characterization. Anesthesiology. 2008;108:1037–46. https://doi.org/10.1097/ALN.0b013e318173f64f.
31. Sudo E, Fukuchi Y, Ishida K, et al. Diffuse aspiration bronchiolitis (DAB) produced in animals by repeated HCl microaspiration. Jpn J Geriat. 1994;31:435–40. (in Japanese)
32. Alluri R, Kutscher HL, Mullan BA, Davidson BA, Knight PR. Open tracheostomy gastric acid aspiration murine model of acute lung injury results in maximal acute nonlethal lung injury. J Vis Exp. 2017;120:54700.
33. Chiang SR, Tang HJ, Chen CH, Chen CC, Lee WY, Chang PC, et al. Acid aspiration provokes the pneumonia caused by multidrug-resistant Acinetobacter baumannii in BALB/c mice. Int J Infect Dis. 2013;17:e454–60.
34. Nagase T, Uozumi N, Ishii S, Kume K, Izumi T, Ouchi Y, Shimizu T. Acute lung injury by sepsis and acid aspiration: a key role for cytosolic phospholipase A2. Nat Immunol. 2000;1(1):42–6.
35. Tavares AH, Colby JK, Levy BD, Abdulnour RE. A Model of self-limited acute lung Injury by unilateral Intra-bronchial acid Instillation. J Vis Exp. 2019;150:e60024. https://doi.org/10.3791/60024.
36. Mendelson CL. The aspiration of stomach contents into the lungs during obstetric anesthesia. Am J Obstet Gynecol. 1946;52:191205.
37. Baron RM, Levy BD, et al. Acute respiratory distress syndrome. Harrison's principles of internal medicine, 20e. Jameson, JL: McGraw-Hill Education; 2018.
38. Thompson BT, Chambers RC, Liu KD. Acute respiratory distress syndrome. N Engl J Med. 2017;377:562–72.
39. Segal BH, et al. Acid aspiration-induced lung inflammation and injury are exacerbated in NADPH oxidase-deficient mice. Am J Physiol Lung Cell Mol Physiol. 2007;292(3):760–8.
40. Matthay MA, Robriquet L, Fang X. Alveolar epithelium: role in lung fluid balance and acute lung injury. Proc Am Thorac Soc. 2005;2(3):206–13.
41. Chen Z, Chen H, Chen F, Gu D, Sun L, Zhang W, Fan L, Lin Y, Dong R, Lai K. Vagotomy decreases the neuronal activities of medulla oblongata and alleviates neurogenic inflammation of airways induced by repeated intra-esophageal instillation of HCl in Guinea pigs. Physiol Res. 2017;66(6):1021–8.

Part III
New Preventive Strategy

Chapter 15
Pharmacological Approach Based on Substance P Theory: Does the Substance P Play a Central Role in Pathogenesis of Dysphagia in Aspiration Pneumonia?

Seiichi Kobayashi and Masaru Yanai

Abstract Aspiration pneumonia is the common cause of death in the elderly that is associated with decreases in both swallowing and cough reflexes. Basal ganglia infarctions predispose these patients to develop pneumonia due to silent aspiration during sleep. Both reflexes are mediated by endogenous substance P released from vagal sensory nerves. Angiotensin-converting enzyme (ACE) inhibitors suppress degradation of substance P and improve both swallowing and cough reflexes. ACE inhibitors can reduce the risk of aspiration pneumonia in selected patients with stroke, particularly in Asian patients. Cilostazol, an antiplatelet agent, is reported to reduce pneumonia in patients with a history of stroke. Banxia Houpo Tang (BHT, Hange-koboku-to in Japanese), a Chinese herbal (Kampo) medicine, can improve the swallowing and cough reflex in the elderly with a history of pneumonia and have beneficial effects on prevention of pneumonia. Antipsychotics can cause impairment of swallowing reflex due to dopamine blocking activity; therefore, antipsychotics should be avoided in elderly patients. We propose to consider pharmacological approach based on substance P theory to the proper subjects.

Keywords Angiotensin-converting enzyme inhibitors · Aspiration pneumonia · Cough reflex · Substance P · Swallowing reflex

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1 Introduction

Pneumonia is a common cause of morbidity and mortality in the elderly. There is a high incidence of aspiration in elderly patients with pneumonia [1–3]. Aspiration is often resulted from impaired swallowing reflex, which allows bacteria-containing oropharyngeal or gastric secretions or both, into to the lower respiratory tract, especially in patients who also have an ineffective cough reflex [4]. The impairment of these reflexes is a potential risk factor for pneumonia in the elderly [5, 6]. These reflexes are mediated by endogenous substance P [7, 8]. Thus, substance P plays a central role in pathogenesis of aspiration pneumonia, and the intervention to regulate substance P may be a novel approach to prevent pneumonia among the elderly.

This chapter focuses on the pathophysiology and pharmacological approach to aspiration pneumonia based on substance P theory.

2 Clinical Feature of Impairment of Protective Reflexes in Patients with Aspiration Pneumonia

Adequate swallowing and cough reflexes in the airway are important, and suppression or absence of these reflexes has been suggested to be a major risk factor of aspiration pneumonia.

In the 1990s, Sekizawa and colleagues demonstrated that both swallowing and cough reflexes were markedly depressed in patients who had suffered from aspiration pneumonia [7, 8]. The swallowing reflex was evaluated by the latency of response that was timed from the injection of 1 mL distilled water into a throat through a thin nasal catheter to the onset of swallowing. Cough reflex was measured during tidal breathing of aerosolized citric acid delivered by an ultrasonic nebulizer. The cough threshold was defined as the concentration at which the patients coughed at least five times. The latent time of swallowing was 1.2 ± 0.1 (mean ± SE) s, and the threshold concentration of citric acid was 2.6 ± 0.4 mg/mL in the controls, whereas patients with a history of aspiration pneumonia had latent time of swallowing longer than 11 s and a threshold concentration of citric acid higher than 180 mg/mL. Patients above these thresholds of both reflexes may be vulnerable to aspiration pneumonia.

The impairment of both reflexes is often observed not only in patients with neurologic dysphagia, such as poststroke [9, 10] or Parkinson's disease [11, 12], but also in patients who have suffered from community-acquired pneumonia without complaint of dysphasia [1]. Kikuchi et al. showed the incidence of silent aspiration during sleep in elderly patients with acute episode of community-acquired pneumonia using a novel technique employing a radioisotope. One mCi of indium^{111} chloride stirred with a paste was fixed to the subject's teeth before sleep. The paste melted in the mouth during sleep. The next morning, scanning of the thorax was performed with a gamma camera, and 71% of patients had a positive scan in the

lung field, meaning that aspiration of saliva into the lower airway occurred during the night. In contrast, among age-matched control subjects, a positive scan was observed in only 10% of them. Although evaluation of aspiration was limited to one night, silent aspiration occurred more frequently in patients with a recent episode of pneumonia than in control subjects. These observations suggest that elderly subjects with a history of recent pneumonia frequently aspirate during sleep and may develop another pneumonia when normal pulmonary defense mechanisms are overwhelmed.

The influence of sleep on the protective reflexes was investigated [13–15]. Severe delay of the swallowing response in the night compared with that in the day was observed in patients with multiple lacunar infarctions [13, 14]. The cough reflex was also depressed during sleep in patients who had a history of aspiration pneumonia [15]. Like the title of a movie "History Is Made at Night," pneumonia may be made at night in the elderly.

Although the swallowing reflex decreases with the advance of age [16], it is unlikely that advanced age by itself explains the impaired protective reflex in older patients with aspiration pneumonia [17].

3 Mechanisms of Swallowing and Cough Reflexes

The first protection against silent aspiration is preserved swallowing function. The swallowing process is commonly divided into oral, pharyngeal, and esophageal phases according to the location of a bolus. The pharyngeal phase of swallowing is involuntary and totally reflexive; therefore, no pharyngeal activity occurs until the swallowing reflex is triggered. This swallowing reflex lasts approximately 1 second and involves the motor and sensory tracts from cranial nerves IX (glossopharyngeus) and X (vagus). The swallowing reflex is also controlled by substance P, which is secreted from nerve endings in the oropharyngeal mucosa. In guinea pig model, capsaicin desensitization inhibits swallowing reflex [18]. Exogenously administered substance P caused a dose-dependent increase in number of swallows, and a specific inhibitor of NK1 receptor reduced it. Administration of capsaicin, an active component of chili peppers, has shown improvement of swallowing reflex in elderly patients [19]. Capsaicin activates transient receptor potential V1 (TRPV1) of nerve endings of C-fibers and releases neurotransmitters including substance P.

Cough is the last defense against silent aspiration. Airway inflammation and inhaled irritant substances stimulate unmyelinated C-fibers of the sensory nerves in the larynx and lower respiratory tract, thus causing the release of neuropeptides. Substance P is a member of tachykinins and is the most important neurotransmitter for cough reflex. Substance P is stored in sensory nerve endings and can be released from sensory nerves in response to various stimuli. Substance P activates rapidly adapting receptors in the larynx and lower respiratory tract, sending impulses to the brainstem.

Enzymes involved in substance P degradation include neutral endopeptidase, kininase II, serine proteases, and mast cell chymase. These regulate the

concentration of substance P in the airway epithelium and control coughing. In guinea pig model, a selective inhibitor of neutral endopeptidase or a specific inhibitor of NK1 receptor (the receptor of substance P) markedly attenuated the cough response [20]. Kininase II is an angiotensin-converting enzyme (ACE); thus ACE inhibitors suppress degradation of substance P. Thus, the increased substance P induces cough response.

Decreased cough reflex is associated with a more serious underlying disorder, such as cerebrovascular diseases. In particular, cerebrovascular diseases with deep cortical infarcts induce decrease in dopamine. Dopamine is synthesized in the substantia nigra, and the reduction in dopamine leads to decreased synthesis of substance P in the cervical ganglia of the vagal sensory nerve. This decrease in substance P impairs the cough and swallowing reflexes. Impairment of swallowing reflex causes aspiration of saliva containing mixed flora from the oropharynx. If aspiration into lower airways happens, a cough should evoke; however, the decrease in substance P also suppresses the cough reflex; thus "silent aspiration" without cough response develops aspiration pneumonia.

In patients suffering from aspiration pneumonia, both swallowing and cough reflexes mediated by endogenous substance P may be impaired. It was reported that the concentration of substance P in induced sputum was decreased in the elderly patients with aspiration pneumonia compared with healthy subjects [21]. Then, ACE inhibitors, which suppress degradation of substance P, can be beneficial through improving cough reflex [22] and swallowing reflex [23] in these patients.

4 Mechanisms of Development of Aspiration Pneumonia Associated with Impaired Protective Reflexes

Stroke is one of the major causes of aspiration pneumonia [24]. Both swallowing and cough reflexes are depressed during the first 2 weeks after the onset of stroke [9]. Impairment of protective reflexes in the airway leads to being a potential risk factor of aspiration pneumonia in patients with cerebral infarction.

Nakagawa et al. demonstrated that basal ganglia strokes predispose elderly patients in a long-term care facility to developing pneumonia owing to silent aspiration during sleep [14]. The incidence of pneumonia was 2.1 times higher in subjects with unilateral basal ganglia infarcts and 3.6 times higher in those with bilateral basal ganglia infarcts than in those without any CT findings in basal ganglia. Swallowing reflex measured by the latency of swallowing response in the night was markedly suppressed in subjects with basal ganglia infarcts, compared with those without infarcts. The percentage of positive scans using indium^{111} chloride was also higher in patients with basal ganglia infarcts than in those without infarcts.

Next, they conducted a prospective observational study in community-residing participants who had had no obvious history of stroke, in order to determine whether subjects with asymptomatic lacunar cerebral infarction are more likely to develop pneumonia [25]. During a 2-year follow-up period, the incidence of pneumonia was

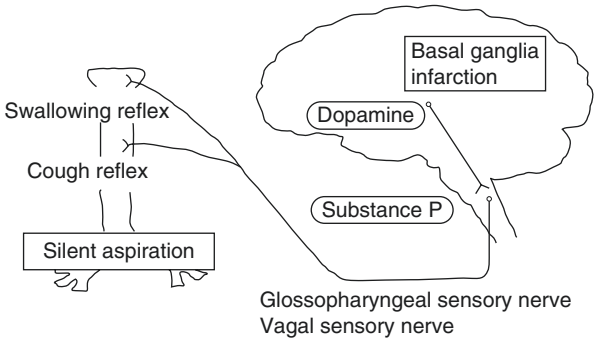

Fig. 15.1 Mechanisms of development of aspiration pneumonia based on substance P theory [5]. In the patient with basal ganglia infarctions, the concentration of substance P is decreased in the vagal sensory nerve and depresses both swallowing and cough reflexes. Impairment of both protective reflexes may increase frequency of silent aspiration and predispose elderly patients to develop aspiration pneumonia

observed significantly higher in subjects with lacunar cerebral infarction with CT scans than those without infarctions (odds ratio, 4.6). Furthermore, deep infarcts were more closely associated with the incidence of pneumonia than superficial infarcts (odds ratio, 5.0).

In 2003, Arai and colleagues proposed that aspiration after stroke may relate to low substance P concentration [26]. The low frequency of spontaneous swallowing was reported in acute stroke patients with low salivary substance P concentration [27].

These findings suggest that basal ganglia infarcts, even without an obvious history of stroke, predispose elderly patients to develop pneumonia owing to silent aspiration during sleep. In these patients the concentration of substance P is decreased in the vagal sensory nerve, resulting in depression of both swallowing and cough reflexes which increases frequency of silent aspiration. Mechanisms of development of aspiration pneumonia based on substance P theory are summarized in Fig. 15.1.

5 Prevention Measures of Aspiration Pneumonia Based on Substance P Theory

From accumulated data regarding swallowing/cough reflexes and aspiration pneumonia in animal experiments and in human studies, several drugs which modulate dopaminergic pathways and/or substance P production/degradation have been investigated whether they are useful to prevent aspiration pneumonia. In this chapter, we also refer to some drugs to prevent recurrence of cerebral infarctions or maneuvers to improve swallowing/cough reflex.

5.1 Angiotensin-Converting Enzyme Inhibitors

Angiotensin-converting enzyme (ACE) inhibitors are widely used in cardiovascular disease. A dry persistent cough is well described as their common adverse effect [28]. Substance P is degraded by ACE, and its action is potentiated by ACE inhibitors. Then, substance P released from nerve endings may accumulate in the upper respiratory tract by blocking substance P degradation and diffuse to rapidly adapting receptors, resulting in increase of cough reflex sensitivity [22]. In a similar way to cough reflex, ACE inhibitors improve swallowing reflex in older patients with aspiration pneumonia [23]. An ACE inhibitor is proven to be useful in prevention of silent aspiration detected by scintigraphy using technetium-99m [29].

In 1998, Sekizawa and colleagues conducted a prospective, observational study on the rate of pneumonia in patient with stroke and demonstrated that ACE inhibitors reduced the risk of pneumonia by about a third, compared with the use of other antihypertensive drugs for hypertension [30]. Arai et al. also reported that the rate of pneumonia was significantly lower in general elderly hypertensive patients given ACE inhibitors than in those treated with calcium channel blockers [31]. Large-scale observational studies were conducted [32, 33]; however, there are some controversies regarding the ACE inhibitor effects on the risk reduction of pneumonia [34]. Recent studies of systematic review and meta-analysis demonstrated that the use of ACE inhibitors can reduce the risk of aspiration pneumonia in selected patients, particularly in Asian subjects and in those with a history of stroke [35, 36]. The prevalence of asymptomatic brain infarction in Asian countries was reported to be greater than in non-Asian countries [37]; thus there may be a lot of the responders for ACE inhibitors in the Asian population.

To prevent aspiration pneumonia, we propose to use ACE inhibitors for blood pressure control in patients who have a history of stroke or showing basal ganglia infarcts on brain images. Moreover, we suggest the use of ACE inhibitors in combination with antibiotic therapy and respiratory care for patients with refractory aspiration pneumonia, although the guidelines have not documented preference of ACE inhibitors [38, 39].

5.2 Amantadine

Delayed triggering of the swallowing reflex occurs in patients with basal ganglia infarctions [14], and an impairment of dopamine metabolism in the basal ganglia is observed in these patients [40]. Administration of levodopa (L-DOPA), a precursor of dopamine, improves the swallowing reflex in patients with basal ganglia infarctions who had a history of aspiration pneumonia [41]. Cabergoline, an ergot derivative, is a potent dopamine receptor agonist of D2 receptors and improves silent aspiration [42].

Amantadine acts as a dopamine releaser from dopaminergic nerve terminals and has been used to treat dyskinesia associated with parkinsonism or aphasia after stroke. Amantadine also improves silent aspiration [42, 43]. Nakagawa and colleagues conducted an open-label, randomized trial of amantadine therapy for prevention of pneumonia in non-bedridden patients with a history of stroke [43]. They showed that the rate of pneumonia was about 20% lower in the amantadine group, compared to those without intervention. Although little evidence is available regarding the efficacy and safety of amantadine therapy for preventing pneumonia, amantadine might be considered for prevention of pneumonia in elderly patients.

5.3 Cilostazol

Cilostazol, an antiplatelet agent, is prescribed for prevention of recurrent cerebral infarction [44]. Administration of cilostazol to patients with cerebral infarction in the chronic stage was reported to reduce the incidence of pneumonia in the Japanese population [45, 46]. According to the subgroup, analysis of a multicenter, randomized, placebo-controlled, double-blind clinical trial of cilostazol was conducted in 1049 subjects, and the incidences of pneumonia during the 3.3-year follow-up were 2.86% in the placebo group and 0.57% in the cilostazol group, showing a significant reduction of a risk of pneumonia in the cilostazol group [46]. Cilostazol upregulates cyclic AMP responsive element binding protein (CREB) phosphorylation, increased tyrosine hydroxylase expression in the substantial nigra, and maintained dopamine and substance P levels [47]. Thus, cilostazol may improve the swallowing reflex by enhancing the expression of tyrosine hydroxylase through the CREB phosphorylation signaling pathway. Treatment with cilostazol for preventing pneumonia may be considered in patients with a history of stroke.

5.4 Banxia Houpo Tang (Hange-koboku-to in Japanese)

Banxia Houpo Tang (BHT, Hange-koboku-to in Japanese), a Chinese herbal (Kampo) medicine, has been used for anxiety disorder, functional dyspepsia, hoarse voice, or some foreign body sensation in the throat and/or esophagus. BHT can increase substance P in the saliva and improve the swallowing and cough reflex in elderly patients with a history of pneumonia [48, 49]. A prospective, observer-blinded, randomized, controlled trial was conducted to evaluate whether BHT prevents pneumonia and pneumonia-related mortality in elderly people [50]. Treatment with BHT reduced the risk of pneumonia and pneumonia-related mortality in elderly patients. Administration of BHT may be considered in the elderly patients for preventing aspiration pneumonia.

5.5 Avoidance of Antipsychotics

Antipsychotics can cause impairment of swallowing reflex due to dopamine blocking activity. Exposure to antipsychotics is associated with an increased frequency and mortality of pneumonia in the elderly [51, 52]. We propose to avoid administration of antipsychotics as far as possible in elderly patients.

5.6 Oral Hygiene

Periodontopathic bacteria can be aspirated into the lower respiratory tract and cause aspiration pneumonia. Cariogenic and periodontal pathogens, dental decay, and poor oral hygiene are identified as potential risk factors for aspiration pneumonia [53]. Oral care can decrease the risk of pneumonia in high-risk populations through reduction of pathogen colonization in dental plaque [54–56]. On the other hand, oral care improves swallowing reflex [57] and cough reflex [58]. Oral care with brushing not only is beneficial for oral hygiene but also improves protective reflexes.

6 Conclusions

Silent aspiration, which is frequently observed in patients with basal ganglia infarctions, is an important risk factor for pneumonia in elderly patients. Both cough and swallowing reflexes are mainly regulated by dopaminergic neurons and substance P-containing sensory nerve; ACE inhibitors and other agents affecting substance P or dopamine metabolism may have beneficial effects on prevention of pneumonia. Since the elderly with frequent pneumonia is often lethal, it is important to identify high-risk or refractory patients and give them appropriate interventions.

References

1. Kikuchi R, Watabe N, Konno T, Mishina N, Sekizawa K, Sasaki H. High incidence of silent aspiration in elderly patients with community-acquired pneumonia. Am J Respir Crit Care Med. 1994;150:251–3.
2. Teramoto S, Fukuchi Y, Sasaki H, Sato K, Sekizawa K, Matsuse T. Japanese study group on aspiration pulmonary disease. High incidence of aspiration pneumonia in community- and hospital-acquired pneumonia in hospitalized patients: a multicenter, prospective study in Japan. J Am Geriatr Soc. 2008;56:577–9. https://doi.org/10.1111/j.1532-5415.2008.01597.x.
3. Almirall J, Rofes L, Serra-Prat M, Icart R, Palomera E, Arreola V, Clave P. Oropharyngeal dysphagia is a risk factor for community-acquired pneumonia in the elderly. Eur Respir J. 2013;41:923–8. https://doi.org/10.1183/09031936.00019012.

4. Sasaki H, Sekizawa K, Yanai M, Arai H, Yamaya M, Ohrui T. New strategies for aspiration pneumonia. Intern Med. 1997;36:851–5.
5. Yamaya M, Yanai M, Ohrui T, Arai H, Sasaki H. Interventions to prevent pneumonia among older adults. J Am Geriatr Soc. 2001;49:85–90.
6. Mandell LA, Niederman MS. Aspiration pneumonia. N Engl J Med. 2019;380:651–63. https://doi.org/10.1056/NEJMra1714562.
7. Sekizawa K, Ujiie Y, Itabashi S, Sasaki H, Takishima T. Lack of cough reflex in aspiration pneumonia. Lancet. 1990;335:1228–9.
8. Nakazawa H, Sekizawa K, Ujiie Y, Sasaki H, Takishima T. Risk of aspiration pneumonia in the elderly. Chest. 1993;103:1636–7.
9. Kobayashi H, Hoshino M, Okayama K, Sekizawa K, Sasaki H. Swallowing and cough reflexes after onset of stroke. Chest. 1994;105:1623.
10. Nakajoh K, Nakagawa T, Sekizawa K, Matsui T, Arai H, Sasaki H. Relation between incidence of pneumonia and protective reflexes in post-stroke patients with oral or tube feeding. J Intern Med. 2000;247:39–42.
11. Ebihara S, Saito H, Kanda A, Nakajoh M, Takahashi H, Arai H, Sasaki H. Impaired efficacy of cough in patients with Parkinson disease. Chest. 2003;124:1009–15.
12. Troche MS, Brandimore AE, Okun MS, Davenport PW, Hegland KW. Decreased cough sensitivity and aspiration in Parkinson disease. Chest. 2014;146:1294–9.
13. Pinto A, Yanai M, Nakagawa T, Sekizawa K, Sasaki H. Swallowing reflex in the night. Lancet. 1994;344:820–1.
14. Nakagawa T, Sekizawa K, Arai H, Kikuchi R, Manabe K, Sasaki H. High incidence of pneumonia in elderly patients with basal ganglia infarction. Arch Intern Med. 1997;157:321–4.
15. Wang HD, Nakagawa T, Sekizawa K, Kamanaka M, Sasaki H. Cough reflex in the night. Chest. 1998;114:1496–7.
16. Leslie P, Drinnan MJ, Ford GA, Wilson JA. Swallow respiratory patterns and aging: presbyphagia or dysphagia? J Gerontol A Biol Sci Med Sci. 2005;60:391–5.
17. Kobayashi H, Sekizawa K, Sasaki H. Aging effects on swallowing reflex. Chest. 1997;111:1466.
18. Jin Y, Sekizawa K, Fukushima T, Morikawa M, Nakazawa H, Sasaki H. Capsaicin desensitization inhibits swallowing reflex in Guinea pigs. Am J Respir Crit Care Med. 1994;149:261–3.
19. Ebihara T, Sekizawa K, Nakazawa H, Sasaki H. Capsaicin and swallowing reflex. Lancet. 1993;341:432.
20. Ujiie Y, Sekizawa K, Aikawa T, Sasaki H. Evidence for substance P as an endogenous substance causing cough in Guinea pigs. Am Rev Respir Dis. 1993;148:1628–32.
21. Nakagawa T, Ohrui T, Sekizawa K, Sasaki H. Sputum substance P in aspiration pneumonia. Lancet. 1995;345:1447.
22. Ebihara T, Sekizawa K, Ohrui T, Nakazawa H, Sasaki H. Angiotensin-converting enzyme inhibitor and danazol increase sensitivity of cough reflex in female Guinea pigs. Am J Respir Crit Care Med. 1996;153:812–9.
23. Nakayama K, Sekizawa K, Sasaki H. ACE inhibitor and swallowing reflex. Chest. 1998;113:1425.
24. Hannawi Y, Hannawi B, Rao CP, Suarez JI, Bershad EM. Stroke-associated pneumonia: major advances and obstacles. Cerebrovasc Dis. 2013;35:430–43. https://doi.org/10.1159/000350199.
25. Nakagawa T, Sekizawa K, Nakajoh K, Tanji H, Arai H, Sasaki H. Silent cerebral infarction: a potential risk for pneumonia in the elderly. J Intern Med. 2000;247:255–9.
26. Arai T, Yoshimi N, Fujiwara H, Sekizawa K. Serum substance P concentrations and silent aspiration in elderly patients with stroke. Neurology. 2003;61:1625–6.
27. Niimi M, Hashimoto G, Hara T, Yamada N, Abo M, Fujigasaki H, Ide T. Relationship between frequency of spontaneous swallowing and salivary substance P level in patients with acute stroke. Dysphagia. 2018;33:414–8. https://doi.org/10.1007/s00455-017-9867-2.
28. Dicpinigaitis PV. Angiotensin-converting enzyme inhibitor-induced cough: ACCP evidence-based clinical practice guidelines. Chest. 2006;129:169S–73S. https://doi.org/10.1378/chest.129.1_suppl.169S.

29. Arai T, Yasuda Y, Takaya T, Toshima S, Kashiki Y, Yoshimi N, Fujiwara H. ACE inhibitors and symptomless dysphagia. Lancet. 1998;352:115–6.
30. Sekizawa K, Matsui T, Nakagawa T, Nakayama K, Sasaki H. ACE inhibitors and pneumonia. Lancet. 1998;352:1069.
31. Arai T, Yasuda Y, Toshima S, Yoshimi N, Kashiki Y. ACE inhibitors and pneumonia in elderly people. Lancet. 1998;352:1937–8.
32. Ohkubo T, Chapman N, Neal B, Woodward M, Omae T, Chalmers J. Effects of an angiotensin-converting enzyme inhibitor-based regimen on pneumonia risk. Am J Respir Crit Care Med. 2004;169:1041–5.
33. van de Garde EM, Souverein PC, van den Bosch JM, Deneer VH, Leufkens HG. Angiotensin-converting enzyme inhibitor use and pneumonia risk in a general population. Eur Respir J. 2006;27:1217–22.
34. Teramoto S, Yamamoto H, Yamaguchi Y, Hanaoka Y, Ishii M, Hibi S, Ouchi Y. ACE inhibitors prevent aspiration pneumonia in Asian, but not Caucasian, elderly patients with stroke. Eur Respir J. 2007;29:218–9.
35. Shinohara Y, Origasa H. Post-stroke pneumonia prevention by angiotensin-converting enzyme inhibitors: results of a meta-analysis of five studies in Asians. Adv Ther. 2012;29:900–12. https://doi.org/10.1007/s12325-012-0049-1.
36. Caldeira D, Alarcao J, Vaz-Carneiro A, Costa J. Risk of pneumonia associated with use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers: systematic review and meta-analysis. BMJ. 2012;345:e4260. https://doi.org/10.1136/bmj.e4260.
37. Fanning JP, Wong AA, Fraser JF. The epidemiology of silent brain infarction: a systematic review of population-based cohorts. BMC Med. 2014;12:119. https://doi.org/10.1186/s12916-014-0119-0.
38. Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, Cooley LA, Dean NC, Fine MJ, Flanders SA, Griffin MR, Metersky ML, Musher DM, Restrepo MI, Whitney CG. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med. 2019;200:e45–67. https://doi.org/10.1164/rccm.201908-1581ST.
39. The Japanese Respiratory Society. The JRS guidelines for management of Pneumonia in adults. 2017.
40. Rodriguez-Grande B, Blackabey V, Gittens B, Pinteaux E, Denes A. Loss of substance P and inflammation precede delayed neurodegeneration in the substantia nigra after cerebral ischemia. Brain Behav Immun. 2013;29:51–61. https://doi.org/10.1016/j.bbi.2012.11.017.
41. Kobayashi H, Nakagawa T, Sekizawa K, Arai H, Sasaki H. Levodopa and swallowing reflex. Lancet. 1996;348:1320–1.
42. Arai T, Sekizawa K, Yoshimi N, Toshima S, Fujiwara H. Cabergoline and silent aspiration in elderly patients with stroke. J Am Geriatr Soc. 2003;51:1815–6.
43. Nakagawa T, Wada H, Sekizawa K, Arai H, Sasaki H. Amantadine and pneumonia. Lancet. 1999;353:1157.
44. Gotoh F, Tohgi H, Hirai S, Terashi A, Fukuuchi Y, Otomo E, Shinohara Y, Itoh E, Matsuda T, Sawada T, Yamaguchi T, Nishimaru K, Ohashi Y. Cilostazol stroke prevention study: a placebo-controlled double-blind trial for secondary prevention of cerebral infarction. J Stroke Cerebrovasc Dis. 2000;9:147–57. https://doi.org/10.1053/jscd.2000.7216.
45. Yamaya M, Yanai M, Ohrui T, Arai H, Sekizawa K, Sasaki H. Antithrombotic therapy for prevention of pneumonia. J Am Geriatr Soc. 2001;49:687–8.
46. Shinohara Y. Antiplatelet cilostazol is effective in the prevention of pneumonia in ischemic stroke patients in the chronic stage. Cerebrovasc Dis. 2006;22:57–60.
47. Zhang N, Miyamoto N, Tanaka R, Mochizuki H, Hattori N, Urabe T. Activation of tyrosine hydroxylase prevents pneumonia in a rat chronic cerebral hypoperfusion model. Neuroscience. 2009;158:665–72. https://doi.org/10.1016/j.neuroscience.2008.10.049.

48. Iwasaki K, Wang Q, Nakagawa T, Suzuki T, Sasaki H. The traditional Chinese medicine banxia houpo tang improves swallowing reflex. Phytomedicine. 1999;6:103–6.
49. Iwasaki K, Cyong JC, Kitada S, Kitamura H, Ozeki J, Satoh Y, Suzuki T, Sasaki H. A traditional Chinese herbal medicine, banxia houpo tang, improves cough reflex of patients with aspiration pneumonia. J Am Geriatr Soc. 2002;50:1751–2.
50. Iwasaki K, Kato S, Monma Y, Niu K, Ohrui T, Okitsu R, Higuchi S, Ozaki S, Kaneko N, Seki T, Nakayama K, Furukawa K, Fujii M, Arai H. A pilot study of banxia houpo tang, a traditional Chinese medicine, for reducing pneumonia- risk in older adults with dementia. J Am Geriatr Soc. 2007;55:2035–40.
51. Dzahini O, Singh N, Taylor D, Haddad PM. Antipsychotic drug use and pneumonia: systematic review and meta-analysis. J Psychopharmacol. 2018;32:1167–81. https://doi.org/10.1177/0269881118795333.
52. Boivin Z, Perez MF, Atuegwu NC, Metersky M, Alvarez CA, Anzueto A, Mortensen EM. Association of atypical antipsychotics and mortality for patients hospitalised with pneumonia. ERJ Open Res. 2019;5:00223–2018. https://doi.org/10.1183/23120541.00223-2018.
53. Azarpazhooh A, Leake JL. Systematic review of the association between respiratory diseases and oral health. J Periodontol. 2006;77:1465–82.
54. Yoneyama T, Yoshida M, Ohrui T, Mukaiyama H, Okamoto H, Hoshiba K, Ihara S, Yanagisawa S, Ariumi S, Morita T, Mizuno Y, Ohsawa T, Akagawa Y, Hashimoto K, Sasaki H. Oral care working group. Oral care reduces pneumonia in older patients in nursing homes. J Am Geriatr Soc. 2002;50:430–3.
55. Kaneoka A, Pisegna JM, Miloro K, Lo M, Saito H, Riquelme LF, LaValley MP, Langmore S. Prevention of healthcare-associated pneumonia with oral care in individuals without mechanical ventilation: a systematic review and meta-analysis of randomized controlled trials. Infect Control Hosp Epidemiol. 2015;36:899–906. https://doi.org/10.1017/ice.2015.77.
56. 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:CD012416. https://doi.org/10.1002/14651858.CD012416.pub2.
57. Yoshino A, Ebihara T, Ebihara S, Fuji H, Sasaki H. Daily oral care and risk factors for pneumonia among elderly nursing home patients. JAMA. 2001;286:2235–6.
58. Watando A, Ebihara S, Ebihara T, Okazaki T, Takahashi H, Asada M, Sasaki H. Daily oral care and cough reflex sensitivity in elderly nursing home patients. Chest. 2004;126:1066–70.

Chapter 16
Roles of Vaccination: Do PPV and Influenza Vaccination Have Preventive Roles in Aspiration Pneumonia?

Masayuki Ishida, Hiroshi Nakaoka, and Konosuke Morimoto

Abstract Aspiration pneumonia is a unit of pneumonia which is diverse in nature. To date, no study evaluating the effects of pneumococcal or influenza vaccines in preventing aspiration pneumonia has been reported, leaving their preventive effects unknown.

The data from our epidemiological studies of pneumonia suggest that each vaccine has the possibility of partially preventing aspiration pneumonia. For prevention of aspiration pneumonia, comprehensive preventive measures, including vaccination, are essential.

Keywords Aspiration pneumonia · PPV · Influenza vaccine

1 Introduction

The burden of pneumonia is known to increase as a result of aging of the society. According to the epidemiological study of community-onset pneumonia (COP) conducted by our group (Adult Pneumonia Study Group-Japan, APSG-J study), elderly patients aged 65 and older accounted for about 70% of all patients with pneumonia aged 15 and older [1].

The nature of pneumonia in elderly people varies depending on the combination of etiology, background factors, and severity, allowing us to consider it as an illness with large diversity. Aspiration may be viewed as one of the crucial etiological factors for this type of pneumonia. At present, however, there are no international

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guidelines that firmly define aspiration pneumonia, nor are there any published papers that clearly demonstrate the effectiveness of vaccination against aspiration pneumonia.

Furthermore, development of aspiration pneumonia is not confined to elderly people. It can also develop in non-elderly people if they have risk factors for aspiration. The pathogens are not confined to *Streptococcus pneumoniae* and *Haemophilus influenzae* isolated from patients with community-acquired pneumonia but involve a wide range of bacteria including the anaerobes in the oral cavity and gram-negative bacilli. There is also chemical pneumonia characterized by poor involvement of pathogens. Thus, aspiration pneumonia is diverse and very difficult to discuss as a single entity.

Vaccination is one of the important tools for prevention of pneumonia. Two pneumococcal vaccines available at present (pneumococcal polysaccharide vaccine [PPV] and pneumococcal conjugate vaccine) are expected to directly prevent pneumonia, and influenza vaccine is expected to have an indirect effect in pneumonia prevention. This chapter will discuss the effects of PPV and influenza in preventing pneumonia in individuals having the risk factors for aspiration, on the basis of the data collected during the APSG-J study.

2 What Is APSG-J Study? [1]

To collect reliable epidemiological information about pneumonia in the aging society, this study was carried out by registering patients with COP (community-acquired pneumonia [CAP] and healthcare-associated pneumonia [HCAP]) managed at hospitals providing the most active acute care in each of the districts, namely, Hokkaido, Chiba, Kochi, and Nagasaki, of Japan (total number of beds, 1805) during the 3-year period from September 2011.

In this study, a target was set at registering all cases of COP visiting each participating hospital, and patients not covered by prospective registration were additionally registered using their medical records. At each participating hospital, the ratio of the number of outpatients to the number of COP patients was determined, and the incidence of COP was estimated from the number of outpatients and the population made public for each healthcare zone concerned.

In total, 3509 patients with pneumonia were registered. Analysis of the data for the period from September 2011 to January 2013 revealed that 57% of all COP patients were aged 75 and older and that 25% were aged 85 and older. The incidence of COP was 16.9 (95% CI 13.6–20.9)/1000 individuals · year, showing a sharp rise after age 65, with the incidence at age 85 and older being 79.3 (95% CI 65.7–95.5)/1000 individuals · year (Fig. 16.1). This incidence was higher than that reported from Western countries even after adjustment for age. Analysis of the data on sputum culture, urinary antigen, and sputum PCR in all cases revealed that *S. pneumoniae* was positive in 19% of all COP cases, with the incidence of

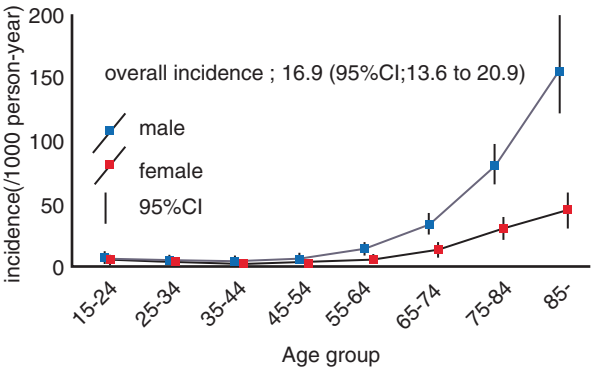

Fig. 16.1 Annual incidences of community-onset pneumonia per 1000 people by age group and gender. The incidence among the male population is shown as a blue square, and the incidence among the female population is shown as a red square. The 95% confidence intervals for each point are shown as vertical lines [1].

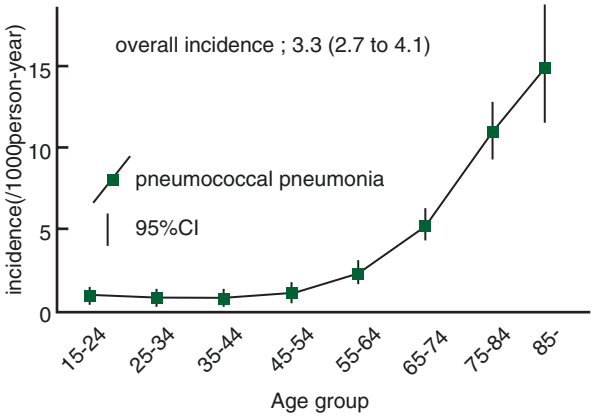

Fig. 16.2 Annual incidences of pneumococcal pneumonia per 1000 people by age group. The incidence among the pneumococcal pneumonia is shown as a green square. The 95% confidence intervals for each point are shown as vertical lines. Source: [1]

S. pneumoniae-positive COP rising sharply from age 65 (Fig. 16.2). These results indicate that pneumonia in general and pneumococcal pneumonia can be positioned as important illnesses in Japan.

3 Pneumonia Possessing the Risk Factors for Aspiration

Various background factors possessed by COP patients were also analyzed during the APSG-J study (Fig. 16.3). This analysis revealed that 1970 patients (56%) possessed risk factors for aspiration, 679 (19%) tested positive for *S. pneumoniae,* and 126 (3.6%) tested positive for influenza virus.

Of all patients possessing the risk factors for aspiration, 282 (14%) were *S. pneumoniae* positive, and 63 (3.2%) were influenza virus positive. Thus, the *S. pneumoniae*-positive rate and the influenza virus-positive rate were significantly low among the patients possessing risk factors for aspiration.

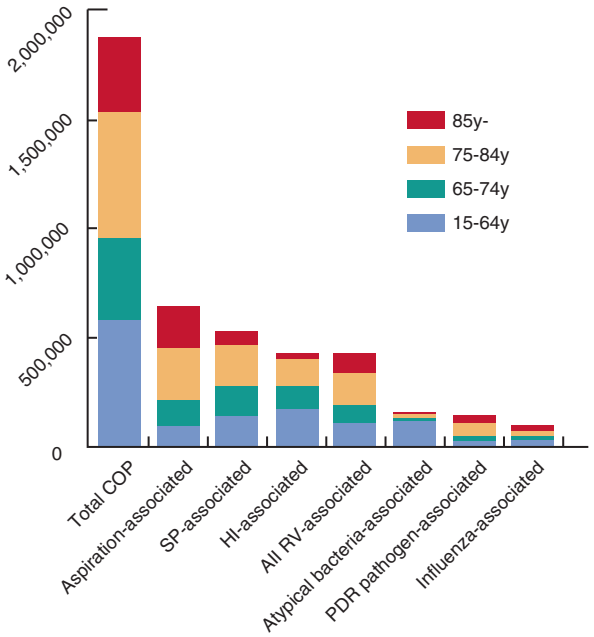

Fig. 16.3 Estimated annual burden of community-onset pneumonia in Japanese adults by clinical and etiological category, 2012. *SP*, *S. pneumoniae*; *HI*, *H. influenzae*; *PDR* potentially drug-resistant; *RV* respiratory virus. Maximum estimates are shown for SP- and HI-associated pneumonia. Source: [1]

4 About PPV

PPV23 is prepared by purification of the capsular polysaccharides constituting the surface of the bacterium of 23 serotypes. Its effect in preventing invasive pneumococcal pneumonia is evident, and the use of this vaccine has been recommended for elderly patients aged 65 and older as well as immunodeficient patients (e.g., patients after splenectomy). Although this vaccine covers a wide range of serotypes, it has a shortcoming in that efficacy is not expected in children younger than2 years (premature in immune function) because this vaccine does not induce memory B cells.

Although numerous studies have been conducted on the pneumonia-preventive effects of PPV23, there has been no consistent view on its efficacy [2]. Under such circumstances, in 2012, a paper by Kawakami et al. demonstrated significant suppression of direct healthcare expenditure by PPV23 vaccination [3]. Subsequently, the vaccination group of infection panel under the Ministry of Health, Labour and Welfare of Japan decided on public financial aid to vaccination for elderly people aged 65 and older, beginning in October 2014. According to the Ministry of Health, Labour and Welfare (MHLW) statistics, the percentage of adults aged 65 and older having received PPV23 vaccination in 2014 through 2017 remained in the order of 30% [4].

In past studies, it was difficult to demonstrate the efficacy of PPV23 against non-invasive pneumococcal pneumonia. This is probably because the efficacy of this 23-valent vaccine (a vaccine against a limited range of pneumococcal pneumonia) was difficult to detect in the analysis setting the outcome as “all types of

Table 16.1 Pneumonia-preventive effects of PPV. Source: [5]

	Adjusted vaccine effectiveness (%)	95% CI
All pneumococcal pneumonia	27.4	3.2–45.6
PPV23 serotypes	33.5	5.6–53.1
PCV13 serotypes	40.1	9.9–60.2

pneumonia" or "all types of pneumococcal pneumonia." We conducted a subanalysis of the data from APSG-J study, focusing on the efficacy of PPV23 against each serotype. The results revealed the estimated successful prevention rate of PPV23 to be 27.4% for all types of pneumococcal pneumonia and 33.5% for pneumonia of the relevant serotypes. This study demonstrated for the first time in the world the effect of PPV23 in preventing pneumonia caused by the serotypes of the pathogen contained in the vaccine (Table 16.1) [5].

With reference to this result, we can estimate that prevention is possible in 27.4% of the 282 *S. pneumoniae*-positive cases having the risk factors for aspiration, i.e., in 77 of such cases. This number corresponds to about 4% of all individuals having the risk factors for aspiration.

Considering the efficacy of pneumococcal vaccine, it is very important under the present status to take into account the serotype. In our study investigating the time course of the vaccine coverage in relation to the serotype of pneumococcal pneumonia, the serotype coverage was also high for *S. pneumoniae* among people accommodated into care facilities [6]. In the above-cited study designed to evaluate the efficacy of PPV, the preventive efficacy tended to be high in people younger than age 75 and against HCAP and airspace pneumonia. Serotype distribution may differ between individuals having the risk factors for aspiration and those without such factors. It may thus be important to further analyze the vaccine coverage by population.

Furthermore, following the recent spread of vaccination among children and adults, serotype substitution (substitution of the serotype of responsible *S. pneumoniae* with a serotype not contained in the vaccine) has been indicated [7]. The percentage of vaccine coverage with the use of PPV is anticipated to decrease year after year from now on, probably resulting in a decrease in the vaccination's impact on pneumonia in general corresponding to the decrease in coverage. A similar trend is reasonably expected also among cases of pneumonia possessing the risk factors for aspiration. It is therefore desirable to develop a vaccine covering new serotypes and a vaccine with new mechanisms of action.

5 Influenza Vaccine

It is known well that influenza infection, including infection secondary to influenza, can lead to pneumonia. In past studies, vaccination against influence was shown to be effective in preventing influenza-associated pneumonia in nearly 60% of all vaccinated people [8, 9]. Assuming that this data can be directly applied to

epidemiology in Japan, simple calculation reveals that there are 63 individuals who have risk factors for aspiration and are influenza virus positive and that suppressive effects are manifested in 56.7% (about 36) of these people, equivalent to about 2% of all people possessing the risk factors for aspiration.

Studies of pneumococcal vaccines revealed that pneumococcal vaccination was often accompanied by simultaneous vaccination against influenza. For this reason, the effects arising from concomitant use of these vaccines have often been pointed out. The current inactivated vaccines still play an important role although their efficacy varies depending on the season, and there are arguments over difference in efficacy depending on age and so on.

6 Conclusions

We estimate that PPV and influenza vaccine can suppress approximately 4% and 2% of pneumonia associated with the risk factors for aspiration, respectively, thus suggesting that aspiration pneumonia can be partially prevented by each of these vaccines. Considering that many of the pneumonia patients having the risk factors for aspiration are at an advanced age, these vaccines may be useful and important as a means of reducing the increasing burden from pneumonia among elderly people. Meanwhile, the efficacy of these vaccines is limited, and combination of these vaccines with other preventive measures without using vaccines is also important.

If serotype substitution advances and the percentage of vaccine-covered serotypes decreases, the effect of pneumococcal vaccination in suppressing pneumonia will also attenuate. It is therefore important to review or expand the vaccine-covered serotypes and to develop new types of vaccine. In devising better vaccination strategy, there are open issues to be addressed, such as analysis of serotype by population and clarification of the efficacy of simultaneous use of influenza vaccine.

References

1. Morimoto K, Suzuki M, Ishifuji T, et al. Adult pneumonia study group-Japan (APSG-J).The burden and etiology of community-onset pneumonia in the aging Japanese population: a multicenter prospective study. PLoS One. 2015;10:eO122247.
2. Moberley S, Holden J, Tatham DP, et al. Vaccines for preventing pneumococcal infection in adults. Cochrane Database Syst Rev. 2013;31(1):CDOOO422. https://doi.org/10.1002/14651858.CDOOO422.pub3.
3. Kawakami K, Ohkusa Y, Kuroki R, et al. Effectiveness of pneumococcal polysaccharide vaccine against pneumonia and cost analysis for the elderly who receive seasonal influenza vaccine in Japan. Vaccine. 2010;28:7063–9.
4. Number of regular immunizations. http://www.mhlw.go.jp/topics/bcg/other/5.html.
5. Suzuki M, Dhoubhadel BG, Ishifuji T, et al. Adult pneumonia study group-Japan (APSG-J). Serotype-specific effectiveness of 23-valent pneumococcal polysaccharide vaccine against

pneumococcal pneumonia in adults aged 65 years or older: a multicentre, prospective, test-negative design study. Lancet Infect Dis. 2017;17:313–21.
6. Sando E, Suzuki M, Morimoto K, et al. Impact of the pediatric 13-valent pneumococcal conjugate vaccine on serotype distribution and clinical characteristics of pneumococcal pneumonia in adults: the Japan pneumococcal vaccine effectiveness study (J-PAVE). Vaccine. 2019;37:2687–93.
7. Weinberger DM, Malley R, Lipsitch M. Serotype replacement in disease after pneumococcal vaccination. Lancet. 2011;378:1962–73.
8. Grijalva CG, Zhu Y, Williams DJ, et al. Association between hospitalization with Community-acquired laboratory-confirmed influenza pneumonia and prior receipt of influenza vaccination. JAMA. 2015;314:1488–97.
9. Suzuki M, Katsurada N, Morimoto K, et al. Effectiveness of inactivated influenza vaccine against laboratory-confirmed influenza pneumonia among adults aged ≥65 years in Japan. Vaccine. 2018;36:2960–7.

Chapter 17
Oral Care: Does Oral Care Have Preventive Roles in Aspiration Pneumonia?

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Abstract Oral care and oral management are important for preventing aspiration pneumonia, as shown by a growing body of scientific evidence. Oral care helps to prevent aspiration pneumonia by reducing oral bacteria, while oral management helps by improving masticatory and rehabilitating functions. Focused oral care in the acute phase is effective in preventing ventilator-associated pneumonia and may help to improve therapeutic outcomes among patients in intensive care. Oral management starts with oral problems being noticed not only by dentists and dental hygienists but also by professionals in other disciplines. The oral health assessment tool is an effective, reproducible, and valid instrument for assessing the oral cavity. In the chronic phase, it is important to understand the characteristics of individual diseases (stroke sequelae, dementia) and take individualized measures in addition to basic oral care techniques. Oral management includes the concept of preventing aspiration pneumonia through function training. Exercises for diminished tongue function and swallowing function help to prevent aspiration pneumonia by improving swallowing function.

Keywords Oral care · Oral management · Oral health assessment tool (OHAT) Functional muscle exercises

1 Introduction

Evidence-based research is increasingly highlighting the effectiveness of oral management for the prevention of respiratory infections such as pneumonia. Preoperative oral care effectively prevents postoperative pneumonia in patients undergoing

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surgery under general anesthesia [1–3], and perioperative oral management reduces the incidence of postoperative pneumonia and febrile episodes [4, 5]. Most acute care hospitals follow the policy of inhospital dental clinic or local dental clinic visits preoperatively, and patients are advised to ensure thorough oral cleansing prior to undergoing surgery under general anesthesia. The clinical path based on preoperative oral management is being prepared in each hospital. Notably, patients who undergo esophageal or head and neck cancer surgery and those with stroke are predisposed to oral dysfunction and dysphagia. Dental prosthetic rehabilitation is necessary to maintain and restore oral and swallowing function to prevent aspiration pneumonia. Notably, the pathomechanism contributing to pneumonia in patients with reduced activities of daily living (ADL) differs from that observed in patients with normal ADL. Daily oral hygiene is difficult in elderly patients and in those with stroke, and the increased salivary bacterial content predisposes these patients to pneumonia. In fact, the rate of detection of oral bacteria is higher in elderly patients who require nursing home services than in elderly patients who can visit a hospital [6].

Swallowing rehabilitation, antimicrobial treatment, and attention to oral hygiene are particularly important in these patients for prevention of pneumonia. This chapter describes the importance of oral care and oral management for the prevention of aspiration pneumonia.

2 Oral Care and Oral Management

In this chapter, we define the terms oral care and oral management. “Oral care” includes toothbrushing or mouth rinsing for oral cavity cleansing.

“Oral management” refers to oral hygiene as well as maintenance and restoration of chewing and swallowing function using oral rehabilitation and dental treatment through the use of prosthesis such as dentures. Oral management aims to maintain optimal oral intake and speech function. Therefore, oral management includes oral hygiene as well as oral function.

Effective oral management requires interprofessional collaboration between physicians, nursing staff, pharmacists, speech therapists, physical therapists, occupational therapists, and nutritionists and is not limited to interventions performed by dentists and dental hygienists.

3 Acute Phase Oral Management

3.1 Oral Management in Intensive Care

For patients in the intensive care unit (ICU), dentists and dental hygienists should check for tooth dislocation and oral mucosa damage, assess potential contamination of inserted tubes, and support nurses as they perform oral care. These suggestions are grounded in the efficacy of oral assessment and care in the ICU for preventing

ventilator-associated pneumonia (VAP), a form of pneumonia which manifests more than 48 hours after intubation [7]. Acute phase oral care can be expected to prevent VAP and postoperative infection and shorten the duration of hospitalization. In a study conducted with patients in a neuroscience critical care unit, oral care (deep oropharyngeal suctioning, brushing the teeth every 12 hours, and swabbing every 4 hours) reduced the yearly incidence of VAP [8]. A randomized controlled trial conducted with patients in the ICU who had suffered a stroke featured an intervention (200 patients) consisting of tooth, tongue, and palate brushing every 8 hours along with tooth, tongue, and palate swabs every 8 hours versus a control (200 patients) consisting of toothbrushing and swabbing when necessary. The intervention reduced the VAP incidence rate from 8.2 to 0.63 per 1000 ventilation days [9]. In a multicenter, retrospective cohort study conducted with patients with intracerebral hemorrhage, an early oral care intervention program, consisting of 5-minute oral care sessions conducted at least three times daily, significantly reduced the incidence of chest infections (control, 35.6%; early intervention, 20.9%; $p = 0.016$) and the use of antibiotics (control, 16.3 vials/patient; early intervention, 6.1 vials/patient; $p = 0.009$), significantly increased the percentage of patients with a Functional Oral Intake Scale score of 7 or "total oral diet with no restrictions" (control, 16.7%; early intervention, 29.5%; $p = 0.001$), and significantly improved activities in daily living and quality of life (modified Rankin Scale score of 5−6; control, 53.3%; early intervention, 39.5%; $p = 0.044$; and Glasgow Outcome Scale score of 1−2; control, 21.1%; early intervention, 5.4%; $p < 0.001$) [10].

As the above studies show, focused oral care for patients in the ICU is effective for preventing VAP and may help to improve therapeutic outcomes.

3.2 Oral Health Assessment Tool (OHAT)

The objectives of oral health assessment are to determine the state of contamination of the oral cavity and to provide numerical feedback when the patient is reassessed to demonstrate any improvement in their oral hygiene. Tools for assessing oral health must be simple to use and should take little time to complete them. Although there are several tools available for assessing oral care, oral health assessment tool developed by Chalmers et al. [11] (Fig. 17.1) in its Japanese version (OHAT-J) is recommended. Once the assessor is familiar with the OHAT, assessments can be conducted in about 1 minute. The OHAT consists of eight oral cavity categories assessed on a three-point scale ranging from healthy (score, 0) to unhealthy (score, 2). The OHAT categories have been shown to be reproducible and valid in medical and nursing practices [12].

The details of each category of the OHAT are described below:

- Lips. Assessment of the lips includes observing the corners of the mouth and the inside of the lips. The corners of the mouth are observed by gently opening the mouth. If the corners are dry or chapped, the category is scored as 1. Redness at the corners may be due to infection by *Candida*. If there is ulceration and associated bleeding, the category is scored as 2.

Resident: _____ Completed by: _____ Date:___/___/___

	Scores – *You can circle individual words as well as giving a score in each category (* if 1 or 2 scored for any category please organize for a dentist to examine the resident)*			
Category	0 = healthy	1 = changes*	2 = unhealthy*	Category scores
Lips	smooth, pink, moist	dry, chapped, or red at corners	swelling or lump, white/red/ ulcerated patch; bleeding/ ulcerated at corners	
Tongue	normal, moist roughness, pink	patchy, fissured, red, coated	patch that is red and/or white, ulcerated, swollen	
Gums and tissues	pink, moist, smooth, no bleeding	dry, shiny, rough, red, swollen, one ulcer/sore spot under dentures	swollen, bleeding, ulcers, white/red patches, generalized redness under dentures	
Saliva	moist tissues, watery and free flowing saliva	dry, sticky tissues, little saliva present, resident thinks they have a dry mouth	tissues parched and red, very little/no saliva present, saliva is thick, resident thinks they have a dry mouth	
Natural teeth Yes/No	no decayed or broken teeth/roots	1-3 decayed or broken teeth/ roots or very worn down teeth	4 + decayed or broken teeth/roots, or very worn down teeth, or less than 4 teeth	
Dentures Yes/No	no broken areas or teeth, dentures regularly worn, and named	1 broken area/tooth or dentures only worn for 1-2 hrs daily, or dentures not named, or loose	more than 1 broken area/tooth, denture missing or not worn, loose and needs denture adhesive, or not named	
Oral cleanliness	clean and no food particles or tartar in mouth or dentures	food particles/tartar/plaque in 1-2 areas of the mouth or on small area of dentures or halitosis (bad breath)	food particles/tartar/plaque in most areas of the mouth or on most of dentures or severe halitosis (bad breath)	
Dental pain	no behavioural, verbal, or physical signs of dental pain	are verbal &/or behavioural signs of pain such as pulling at face, chewing lips, not eating, aggression	area physical pain signs (swelling of cheek or gum, broken teeth, ulcers), as well as verbal &/or behavioural signs (pulling at face, not eating, aggression)	
☐ Organize for resident to have a dental examination by a dentist ☐ Resident and/or family/guardian refuses dental treatment ☐ Complete Oral Hygiene Care Plan and start oral hygiene care interventions for resident ☐ Review this resident's oral health again on Date:___/___/___				TOTAL ___ SCORE: 16

Fig. 17.1 Oral health assessment tool (OHAT). OHAT consists of eight categories assessed on a three-point scale ranging from healthy (score: 0) to unhealthy (score: 2)

- Tongue. The assessor must check the dorsal surface and lateral borders of the tongue for ulceration. If the tongue is coated, the category is scored as 1 regardless of the volume, properties, or color of the coating (Fig. 17.2a). If there are ulceration and associated bleeding, candidal white patches are present, or there is overall swelling of the tongue, the category is scored as 2.
- Gums and tissues. The gums and buccal mucosa are combined into a single category. Swelling or redness of the gums is scored as 1 if present in the gums of six or fewer teeth and scored as 2 if present in the gums of seven or more teeth. If there are ulcers in the gums or buccal mucosa, there is periodontitis-associated tooth mobility, or there are any oral mucosal diseases such as candidiasis of the buccal mucosa or oral lichen planus, the category is scored as 2 (Fig. 17.2b).

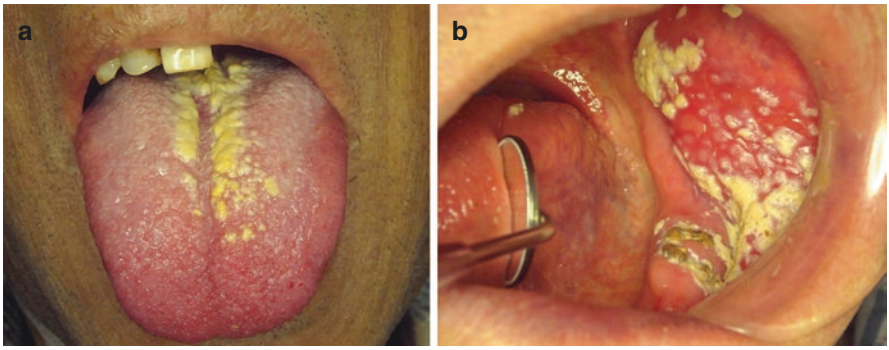

Fig. 17.2 (**a**) Coating on dorsal surface of the tongue. (**b**) Candidiasis of the buccal mucosa

- Saliva. If the oral cavity is moist, the category is scored as 0. If there is little saliva present and the mucosa is sticky or the patient's saliva is foamy, the category is scored as 1. If there is very little saliva and the mouth is dry, the category is scored as 2. If the patient is capable of communication, the following subjective assessment may also be performed: if the patient thinks their mouth is slightly dry, the category is scored as 1; if the patient responds that their mouth is dry, the category is scored as 2.
- Natural teeth. Natural teeth are assessed in terms of decay and roots. If there is no decay and no broken teeth/roots or if the patient has no natural teeth and wears upper and lower dentures, the category is scored as 0. The category is scored as 1 if there are three or fewer decayed or broken teeth/roots and scored as 2 if there are four or more.
- Dentures. If the patient wears dentures regularly in daily life, the category is scored as 0. The category is scored as 1 if there is one broken/damaged area in the patient's dentures and scored as 2 if there are two or more such areas. If the patient wears dentures only 1−2 hours a day due to improper fit, the category is scored as 1. If improper denture fit causes the patient not to wear them at all, the category is scored as 2.
- Oral cleanliness. This category assesses not only plaque and tartar but also food particles. The oral cavity is divided into six areas (maxillary/mandibular anterior teeth and molars on each side). If there is plaque, tartar, or food particles in 1−2 areas, the category is scored as 1 and scored as 2 if three or more areas are involved. Mild halitosis is scored as 1, while severe halitosis is scored as 2.
- Dental pain. Because some patients cannot express their own oral pain, it is assessed with a face scale. If the patient pulls at their face, chews their lips, does not eat, or acts aggressively due to oral pain, the category is scored as 1. The category is scored as 2 if there are physical signs of pain such as swelling of the cheek or gums, broken teeth, ulcers, or subgingival abscess. Verbal and behavioral signs are also scored as 2.

Oral management starts with oral problems being noticed by professionals in a variety of disciplines. OHAT is a reproducible, valid, and effective method for assessing the oral cavity in medical practice.

4 Oral Management for Elderly Persons Requiring Long-Term Care

Elderly persons requiring long-term care sometimes cannot care for themselves due to diminished activities of daily living and therefore require a caregiver. A study conducted with bedridden elderly patients hospitalized for chronic illnesses found that when these patients received proactive oral care (toothbrushing), fevers at 1 month after admission and pneumonia during hospitalization occurred less frequently [13].

4.1 Basic Oral Care Techniques

Oral care is performed in the following order: oral moisturizing, softening of dried contaminants, cleaning of tooth surfaces, removal of softened contaminants, swabbing, and oral moisturizing. In addition to these basic techniques, the oral cavity is suctioned as appropriate during care to prevent aspiration of contaminated saliva and water.

Oral moisturizing. Patients who require oral care often suffer from dry lips and/or mouth. First, the lips and mouth are moistened with a moisturizer or mouthwash and then cleaned. The lips are moisturized first to prevent laceration of the lips and corners of the mouth caused by opening of the mouth. An oral moisturizer is applied to the lips and then to the dry oral mucosa.

Softening of dried contaminants. In the event of severe dry mouth, dried contaminants are softened via humidification. Oral moisturizer is applied to dried desquamated epithelium and phlegm on the oral mucosa to soften them. After the moisturizer is applied, desquamated epithelium requires several minutes to soften, during which time tooth surfaces are cleaned.

Cleaning of tooth surfaces. A soft toothbrush is used for patients with bleeding tendency or severe pain. An interdental brush is also used as necessary.

Removal of softened contaminants. Once brushing is completed, care is performed, starting with the moisturized mucosa. Once contaminants have been softened with oral moisturizer, they are removed by brushing them out from the back of the oral cavity toward the opening of the patient's mouth using a sponge brush. The tongue is cleaned from back to front with a tongue brush applied with light pressure.

Swabbing and oral moisturizing. Oral care results in a temporary increase in the number of oral bacteria. Aspiration of contaminated secretions may cause pneumonia; therefore, contaminants must be collected properly. Patients who are capable of

gargling are asked to gargle. Patients who cannot gargle or are at a high risk of aspiration should not be forced to gargle. Instead, oral bacteria can be collected by wiping tooth surfaces and oral mucosa with oral cleansing wipes. In the event of severe dry mouth, swabbing and oral moisturizing are concluded by lightly applying oral moisturizer to the patient's lips and oral cavity.

4.2 Precautions in Oral Care for Patients with Stroke

Oral care for patients with stroke involves consideration of the degree of sequelae of stroke and includes assessment of the patient's level of consciousness and their activities of daily living. In addition, patients with stroke are at risk of dysphagia which manifests in 50% of cases immediately after stroke. However, the prevalence of poststroke dysphagia decreases to roughly 20% at 2 weeks and to roughly 10% at 6 months [14]. If the patient has dysphagia, caution is required regarding aspiration of secretions due to oral care. First, rather than lying faceup, the patient should be as close to a seated position as possible. During oral care, suctioning is performed as appropriate. Patients receiving non-oral nutrition are susceptible to dry mouth due to mouth breathing and dehydration. In addition, diminished oral function increases susceptibility to adhesion of dried desquamated epithelium and thickened tongue coating. Patients with stroke often require not only oral care but also diligent moisturization. Assessment of hypoesthesia and movement disorder of the oral cavity and pharynx is also important for patients with stroke. If the patient has palsy in their arms, then confirm whether they can brush with their dominant hand. If the patient's dominant hand is completely paralyzed, a change in handedness is considered. If the patient is incapable of finer movements, use of an electric toothbrush is sometimes effective. For patients who are completely incapable of self-care, a caregiver is instructed on how to perform care.

4.3 Precautions in Oral Care for Patients with Dementia

Precautions for oral care for patients with dementia depend on the stage of dementia.

In the early stage of dementia, patients may sometimes be incapable of sufficiently cleaning their oral cavities despite being able to brush their own teeth and thus potentially have oral health problems. Patients in this stage of dementia are still capable of receiving dental treatment. Therefore, teeth that require extraction or other treatment should be proactively reported to a dentist. The chief symptoms of dementia are memory impairment and executive function disorder, meaning that oral care does not pose a great risk of aspiration.

In the middle stage of dementia, cognitive function declines further, often requiring caregivers to perform oral care. If a patient sees a toothbrush but does not understand what it is (semantic memory impairment), the patient may accept care if they

Table 17.1 Characteristics of dementia by stage

	Characteristics	Reasons for refusing oral care
Early	Patient cannot brush their teeth sufficiently even if they can brush on their own	Patient does not understand the need for oral care Previous unpleasant experiences Patient does not comprehend oral care itself
	Can (sometimes) receive dental treatment	
	Risk of aspiration is not so high	
Middle	Patient no longer able to brush their teeth on their own	
	Risk of aspiration gradually increases (determine severity of dysphagia)	
Late	Patient has difficulty opening their mouth or keeping their mouth open	Delirium, drowsiness Difficulty opening the mouth or keeping the mouth open due to tension of the lips/cheek or abnormal bite
	Risk of aspiration is high (adjust patient's posture, and prepare an aspirator)	

are shown the act of toothbrushing and are given a chance to try brushing themselves. The gradually increasing risk of aspiration makes it important to determine the severity of the patient's dysphagia.

In the late stage of dementia, not only cognitive function but all the other activities decrease as well, and the risk of aspiration is extremely high. Therefore, it is necessary to adjust the patient's posture and prepare for suctioning. Dysphagia is observed in 13−57% of patients with dementia [15]. As dementia progresses, dysphagia manifests more frequently. Thus, particular caution is required regarding aspiration in patients with severe dementia (Table 17.1).

Dementia is broadly divided into Alzheimer's disease (AD), vascular dementia (VaD), dementia with Lewy bodies (DLB), and frontotemporal dementia (FTD). Understanding their respective characteristics is helpful when performing oral care.

AD involves diminished cognition and understanding, which may render the patient incapable of comprehending oral care itself. In addition, due to thinking and information processing being slowed down, it takes patients time to comprehend what is happening. The key is to introduce oral care in a systematic fashion without rushing the patient.

In VaD, cognitive function is relatively intact compared to other types of dementia. However, VaD often involves the loss of oral sensation and paralysis, thus requiring consideration of irritation in the oral cavity and myotonia around the oral cavity.

DLB is often accompanied by bradykinesia, bent posture, and other symptoms of Parkinson's disease. Some patients demonstrate drug hypersensitivity, which may result in delirium and drowsiness. In addition, dopamine deficiency diminishes the cough reflex, thereby increasing the risk of silent aspiration.

FTD involves preferences for specific behaviors and places, thus requiring consideration of when and where oral care is to be performed. Patients with FTD

Table 17.2 Characteristics of dementia by type

	Factors	Main characteristics
AD	Reduced appetite	Not brushing teeth voluntarily
	Reduced comprehension	Not comprehending toothbrushing itself
	Disorientation Executive function disorder	Not knowing how to use a toothbrush Inability to start toothbrushing
VaD	Movement/sensory disorder	Lip/cheek tension, abnormal bite Difficulty opening mouth/keeping mouth open
		Loss of oral sensation, oral irritation
DLB	Parkinson's symptoms	Bradykinesia, bent posture
	Drug hypersensitivity	Delirium, drowsiness
	Dopamine deficiency	High risk of silent aspiration
FTD	Stereotyped behavior Disinhibition	Brushing teeth only in a certain environment Irritability, oppositional behavior

sometimes lash out at anything that deviates from the norm. Therefore, oral care for them requires a solid understanding of their behaviors (Table 17.2).

5 Preventing Aspiration Pneumonia with Swallowing Muscle Exercises

Safe and effective swallowing involves the coordinated action of several muscles. Bolus transport from the oral cavity into the pharynx requires dynamic lingual deformation and movement. Bolus propulsion into the upper esophagus causes complete obliteration of the pharyngeal cavity by the tongue that pushes against the contracting posterior pharyngeal wall. Simultaneous complex activity of the extrinsic and intrinsic muscles of the tongue causes lingual deformation [16]. The upper esophageal sphincter (UES) opens via anterior-superior traction of the hyoid and larynx secondary to suprahyoid muscle contraction along with cricopharyngeal muscle relaxation [17]. Swallowing muscle function is impaired in patients with stroke, Parkinson's disease, and sarcopenia among other such conditions, which causes oropharyngeal dysphagia with consequent aspiration pneumonia. A swallowing exercise protocol is essential in a clinical setting to strengthen swallowing muscles and improve swallowing function in these patients.

5.1 Exercises to Improve Suprahyoid Muscle Strength: Jaw-Opening Exercise

Jaw movements include opening and closing, as well as lateral movements of the jaw. Jaw opening involves suprahyoid and lateral pterygoid muscle contraction. Notably, suprahyoid muscle contraction elevates the hyoid during swallowing, and

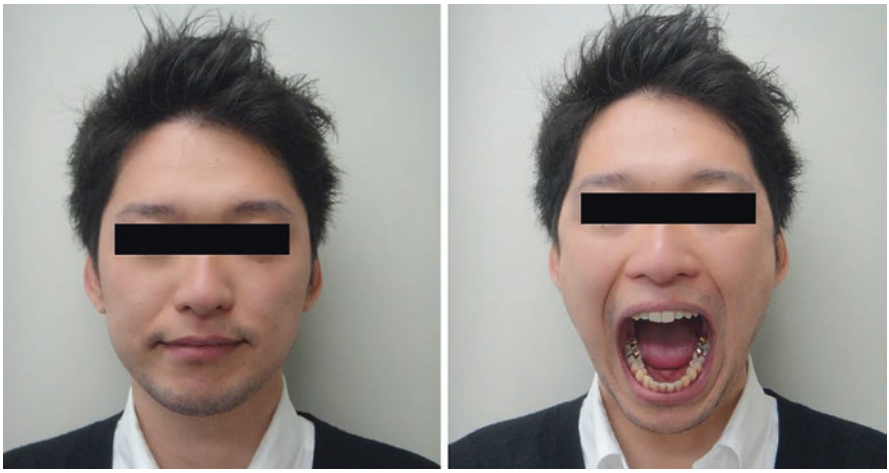

Fig. 17.3 Jaw-opening exercise. Subjects were asked to hold the jaw in the maximally opened position for 10 seconds. Each exercise set involved 5 repetitions of this 10-second motion with a 10-second rest period between each contraction. Each patient performed 2 sets daily

contraction of individual suprahyoid muscles (the anterior digastric, geniohyoid, and mylohyoid) causes jaw depression. This essentially means that the muscles involved with jaw opening elevate the hyoid. Based on this coordinated anatomical activity, we developed a jaw-opening muscle strengthening exercise protocol that involves two daily sets (five repetitions/set) of maintaining maximal jaw opening for 10 seconds [18] (Fig. 17.3). Compared with the pre-intervention status, we observed significantly improved elevation of the hyoid, extent of UES opening, and pharyngeal bolus clearance time, 4 weeks after initiating these exercises. These results suggest that jaw-opening exercises can improve swallowing function in some patients.

5.2 Exercises to Improve Tongue Muscle Strength: Tongue-Pressure Resistance Training

The tongue plays an important role in the oral stage of swallowing, and tongue pressure is a useful index of tongue function. Lifting the tongue against the palate and elevating the floor of the mouth floor generate tongue pressure. The generation of tongue pressure involves tongue elevation via the action of extrinsic and intrinsic tongue muscles and elevation of the floor of the mouth following suprahyoid muscle contraction [19]. Pushing the tongue against the palate to generate pressure simultaneously enhances tongue and suprahyoid muscle function. We describe the effects of tongue-pressure resistance training (TPRT) in this study [20]. Participants were instructed to push their entire tongue against the palate with as much force as possible for 10 seconds with their mouths closed (Fig. 17.4), followed by a period of

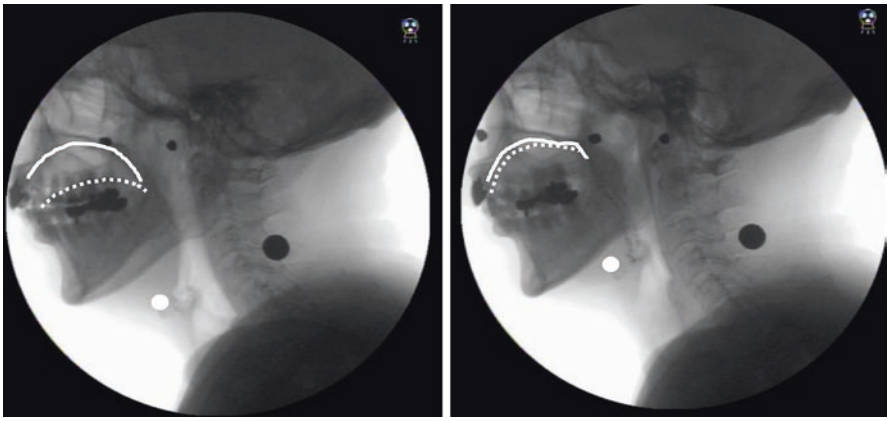

Fig. 17.4 Tongue-pressure resistance training. The straight line is the palate, the dashed line is the tongue surface, and the white circles represent the hyoid bone. The left panel shows the resting position. The right panel shows the elevated hyoid with the tongue pushing against the palate as hard as possible. Tongue-pressure resistance training is carried out as followed; Participants is instructed to push their tongues against the palate as hard as possible with their mouths closed for 10 seconds, then resting for 10 seconds. A set consisted of five consecutive exercises and resting periods; two sets per day were performed for a month

rest for 10 seconds. This activity of exercise and subsequent rest was repeated five times as a set, and participants performed two sets a day for a month. We observed that TPRT improved tongue pressure, the oral diadochokinetic rate (measured by repetition of syllables /ta/ and/ka/ as an index of tongue dexterity), anterior and superior hyoid elevation, and swallowing function. We conclude that TPRT could simultaneously improve tongue and suprahyoid muscle function.

6 Conclusion

Oral care and management have a critical role in preventing aspiration pneumonia by reducing oral bacteria and improving oral and swallowing functions. Oral health assessment tool (OHAT) is an effective and valid tool for assessing the oral cavity by various medical staff. Oral management includes the functional exercises. Exercises for tongue and swallowing function help to prevent aspiration pneumonia by improving swallowing muscle function.

References

1. Akutsu Y, Matsubara H, Shuto K, Shiratori T, Uesato M, Miyazawa Y, et al. Pre-operative dental brushing can reduce the risk of postoperative pneumonia in esophageal cancer patients. Surgery. 2010;147:497–502.

2. AJ DR 2nd, Ladowski JS, Dillon TA, Justice JW, Peterson AC. Chlorhexidine gluconate 0.12% oral rinse reduces the incidence of total nosocomial respiratory infection and nonprophylactic systemic antibiotic use in patients undergoing heart surgery. Chest. 1996;109:1556–61.
3. Bergan EH, Tura BR, Lamas CC. Impact of improvement in preoperative oral health on nosocomial pneumonia in a group of cardiac surgery patients: a single arm prospective intervention study. Intensive Care Med. 2014;40:23–31.
4. Kobayashi Y, Matsuo K, Watanabe R, Fujii W, Kanamori D, Nagata C, et al. The Oral environment in patients under Peri-operative Oral functional management and its intervention effects in our hospital. Jpn J Gerodontol. 2013;28:69–78.
5. Senoo H, Nakano Y, Tokumiya M, Otani M. Efficacy of professional perioperative oral care for elderly patients with femur fractures. J Jpn Soc Dent Med Comp Patient. 2015;24:9–14.
6. Russell SL, Boylan RJ, Kaslick RS, Scannapieco FA, Katz RV. Respiratory pathogen colonization of the dental plaque of institutionalized elders. Spec Care Dentist. 1999;19:128–34.
7. Scannapieco FA, Stewart EM, Mylotte JM. Colonization of dental plaque by respiratory pathogens in medical intensive care patients. Crit Care Med. 1992;20:740–5.
8. Powers J, Brower A, Tolliver S. Impact of oral hygiene on prevention of ventilator-associated pneumonia in neuroscience patients. J Nurs Care Qual. 2007;22:316–21.
9. Fields LB. Oral care intervention to reduce incidence of ventilator-associated pneumonia in the neurologic intensive care unit. J Neurosci Nurs. 2008;40:291–8.
10. Takahata H, Tsutsumi K, Baba H, Nagata I, Yonekura M. Early intervention to promote oral feeding in patients with intracerebral hemorrhage: a retrospective cohort study. BMC Neurol. 2011;11:6. https://doi.org/10.1186/1471-2377-11-6.
11. Chalmers JM, King PL, Spencer AJ, Wright FA, Carter KD. The oral health assessment tool -validity and reliability. Aust Dent J. 2005;50:191–9.
12. Matsuo K, Nakagawa K. Reliability and validity of the Japanese version of the oral health assessment tool (OHAT-J). J Jpn Soc Disabil Oral Health. 2016;37:1–7.
13. Matsusaka K, Ohi A, Tahata K, Shimizu A, Numata M, Ohmiya R, et al. Addition of oral cavity brushing and rehabilitation reduced fever in tube-fed patients. Geriatr Gerontol Int. 2013;13:1082–4. https://doi.org/10.1111/ggi.12088.
14. Smithard DG. Swallowing and stroke. Neurological effects and recovery. Cerebrovasc Dis. 2002;14:1–8.
15. Alagiakrishnan K, Bhanji RA, Kurian M. Evaluation and management of oropharyngeal dysphagia in different types of dementia: a systematic review. Arch Gerontol Geriatr. 2013;56:1–9. https://doi.org/10.1016/j.archger.2012.04.011.
16. Felton SM, Gaige TA, Reese TG, Wedeen VJ, Gilbert RJ. Mechanical basis for lingual deformation during the propulsive phase of swallowing as determined by phase-contrast magnetic resonance imaging. J Appl Physiol. 2007;103:255–65.
17. Cook IJ, Dodds WJ, Dantas RO, et al. Opening mechanisms of the human upper esophageal sphincter. Am J Phys. 1989;257:G748–59.
18. Wada S, Tohara H, Iida T, Inoue M, Sato M, Ueda K. Jaw opening exercise for insufficient opening of upper esophageal sphincter. Arch Phys Med Rehabil. 2012;93:1995–9. https://doi.org/10.1016/j.apmr.2012.04.025.
19. Hori K, Taniguchi H, Hayashi H, Magara J, Minagi Y, Li Q, et al. Role of tongue pressure production in oropharyngeal swallow biomechanics. Physiol Rep. 2013;1:e00167. https://doi.org/10.1002/phy2.167.
20. Namiki C, Hara K, Tohara H, Kobayashi K, Chantaramanee A, Nakagawa K, et al. Tongue-pressure resistance training improves tongue and suprahyoid muscle functions simultaneously. Clin Interv Aging. 2019;22(14):601–8. https://doi.org/10.2147/CIA.S194808.

Chapter 18
Physical Therapy: Does Physical Therapy Have Therapeutic Roles in Aspiration Pneumonia?

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Abstract Aspiration pneumonia is a common disease that frequently occurs in older patients. Most patients with aspiration pneumonia have swallowing disability and develop hospital-acquired disability. Frequently, patients have difficulty returning home, and they often require long-term hospitalization. Recently, the effect of rehabilitative management including physical and pulmonary rehabilitation for aspiration pneumonia was reported. Several studies showed that early rehabilitation was associated with reduced mortality and early hospital discharge after aspiration pneumonia. Physical therapy is recommended to improve clinical outcomes, including physical and swallowing function in older patients with aspiration pneumonia.

Keywords Aspiration pneumonia · Rehabilitation · Oral intake · Mortality

1 Introduction

Aspiration pneumonia (AP) is a common, but potentially serious, disease that frequently occurs in older patients [1]. In Japan, older people comprise a high percentage of home care patients and residents of medical and nursing care facilities. They account for a large proportion of nursing- and healthcare-associated pneumonia (NHCAP) cases and are at high risk of AP. The condition NHCAP was proposed to adapt the concept of healthcare-associated pneumonia to the Japanese medical and nursing care insurance system, and it overlaps to a large extent with AP [2]. However, the classification of AP, which depends on its etiology, differs from that which depends on where the patient acquired the condition. Although the definition of AP can vary depending on researchers and clinicians [3], the Japanese Respiratory

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Society guidelines define AP as pneumonia that develops in patients in whom dysphagia and aspiration is known to occur [2].

Older patients with AP often develop hospitalization-associated disability that can lead to physical decline [4]. Most patients with AP, particularly the elderly, have dysphagia and difficulty with oral intake [5] and malnutrition [6]. Indeed, AP is frequently fatal in such patients. Rehabilitative management including early physical therapy and pulmonary rehabilitation can potentially improve clinical outcomes of older patients with AP. We review the available literature concerning rehabilitative management for aspiration pneumonia in older patients.

2 Search Strategy

We searched research articles focusing on patients older than 60 years who had AP (including suspected cases). With respect to rehabilitative management, we included physical and pulmonary rehabilitation. We searched for relevant articles published until October 2019 using PubMed Central. Combinations of the terms "aspiration pneumonia," "rehabilitation" or "physiotherapy" or "exercise" or "physical therapy" or "early ambulation," and "old" or "elderly" or "geriatric" or "aged" were used to search titles and abstracts. We included observational and interventional studies. Non-English-language publications and abstracts were excluded. Using this search process, we found five relevant articles (Table 18.1).

Table 18.1 Studies investigating effect of physical therapy after aspiration pneumonia

Authors and year	Study design	Number of participants	Participants' age	Intervention	Outcome measures
Chigira et al. 2015 [7]	Prospective	71	>65	Early physical rehabilitation, started within 2 days of admission	Functional Independence Measure, admission period
Yagi et al. 2016 [8]	Retrospective	112,558	>60	Early rehabilitation, started within 7 days of admission	Barthel Index
Miyauchi et al. 2019 [9]	Retrospective	125	>65	Early mobilization by physical therapists, within 3 days of admission	Total oral intake, Oral Intake Scale score
Kim et al. 2015 [10]	Retrospective	1058	>65	Physical rehabilitation	Katz ADL index, 30-day readmission
Momosaki et al. 2015 [11]	Retrospective	68,584	>70	Early physical rehabilitation, started within 3 days of admission	30-day mortality

3 Physical and Pulmonary Rehabilitation

Hospital admission is considered a health risk for elderly patients with AP. Aspiration pneumonia induced muscle atrophy in the respiratory, skeletal, and swallowing systems [12]. Diaphragmatic atrophy may weaken the force of cough to expectorate sputum or mis-swallowed contents. Skeletal muscle atrophy may cause secondary sarcopenia. The atrophy of swallowing muscles may weaken the swallowing function. Muscle atrophy could be a therapeutic target of aspiration pneumonia. Bed rest in the acute phase induces mobility decline and activities of daily living (ADL) decline (hospitalization-associated disability) [13]. Hospitalization-associated disability can lead to cognitive disorders, other complications, extension of hospitalization, difficulty in returning home, quality of life decline, and death.

Generally, acute-phase physical rehabilitation programs for elderly patients with AP comprise early mobilization, range-of-motion exercises, self-care exercises, and muscle strength and endurance training, all of which have the potential to decrease posthospital syndrome and hospital-acquired physical deconditioning. In acute rehabilitation, patients with AP are instructed to sit in a wheelchair during the daytime. Standing and gait training are introduced according to the patient's condition. These rehabilitation methods are feasible and effective for almost all geriatric patients with AP, regardless of the severity of pneumonia [7].

Yagi et al. showed that 71% of elderly AP patients with hospitalization-associated disability did not have improved ADL scores during hospitalization [8]. However, the study showed that early rehabilitation improved ADL significantly (odds ratio, 1.6). Early rehabilitation might prevent ADL decline during hospitalization in patients with AP. Miyauchi et al. reported that early mobilization by a physical therapist is associated with improved total oral intake in patients with sarcopenic dysphagia after pneumonia [9]. Early mobilization by physical therapists to enhance total oral intake may play an important role in improving the level of consciousness and preventing delirium [14]. Also, early mobilization enhances sitting ability for oral intake. Changing the patient's head position or body posture can relieve dysphagia symptoms and improve or ease swallowing [15]. Hyperextension of the neck during bed rest causes mouth opening and xerostomia, particularly in patients with altered sensorium. Poor oral health status was associated with poor oral intake ability prognosis in patients with pneumonia [16], and so early mobilization probably helps in mouth closing and maintaining healthy oral status. Prone posture removes the weight-bearing load on the neck. Early mobilization might contribute to preventing muscle weakness and loss of muscle mass associated with poor oral intake. Furthermore, Kim et al. showed that hospital-based physical therapy helps to reduce the 30-day hospital readmission rate of acutely ill older adults with pneumonia and declining physical function [10].

In pulmonary rehabilitation for acute patients with AP, positioning, postural drainage, sputum elimination assistance, respiration training guidance, and range-of-motion exercises of the upper limbs are conducted. These programs have the potential to decrease risk of mortality. We reported that early rehabilitation,

including pulmonary rehabilitation for acute patients with AP, was associated with a reduction in 30-day inhospital mortality using a nationwide administrative database [11]. Our analysis showed that the early rehabilitation group had a significantly lower inhospital mortality rate.

4 Conclusion

For the treatment of geriatric patients with AP, tailored rehabilitative management is important. Rehabilitative management including early physical and pulmonary rehabilitation is beneficial for older patients with AP.

References

1. Teramoto S, Yoshida K, Hizawa N. Update on the pathogenesis and management of pneumonia in the elderly-roles of aspiration pneumonia. Respir Investig. 2015;53:178–84. https://doi.org/10.1016/j.resinv.2015.01.003.
2. Kohno S, Imamura Y, Shindo Y, Seki M, Ishida T, Teramoto S, et al. Clinical practice guidelines for nursing- and healthcare-associated pneumonia (NHCAP). Respir Investig. 2013;51:103–26. https://doi.org/10.1016/j.resinv.2012.11.001.
3. Komiya K, Ishii H, Kadota J. Healthcare-associated pneumonia and aspiration pneumonia. Aging Dis. 2014;6:27–37. https://doi.org/10.14336/AD.2014.0127.
4. Covinsky KE, Pierluissi E, Johnston CB. Hospitalization-associated disability: "she was probably able to ambulate, but I'm not sure". JAMA. 2011;306:1782–93. https://doi.org/10.1001/jama.2011.1556.
5. Manabe T, Teramoto S, Tamiya N, Okochi J, Hizawa N. Risk factors for aspiration pneumonia in older adults. PLoS One. 2015;10:e0140060. https://doi.org/10.1371/journal.pone.0140060.
6. Sura L, Madhavan A, Carnaby G, Crary MA. Dysphagia in the elderly: management and nutritional considerations. Clin Interv Aging. 2012;7:287–98. https://doi.org/10.2147/CIA.S23404.
7. Chigira Y, Takai T, Igusa H, Dobashi K. Effects of early physiotherapy with respect to severity of pneumonia of elderly patients admitted to an intensive care unit: a single center study in Japan. J Phys Ther Sci. 2015;96:2053–6. https://doi.org/10.1589/jpts.27.2053.
8. Yagi M, Yasunaga H, Matsui H, Fushimi K, Fujimoto M, Koyama T, et al. Effect of early rehabilitation on activities of daily living in patients with aspiration pneumonia. Geriatr Gerontol Int. 2016;16:1181–7. https://doi.org/10.1111/ggi.12610.
9. Miyauchi N, Nakamura M, Nakamura I, Momosaki R. Effect of early versus delayed mobilization by physical therapists on oral intake in patients with sarcopenic dysphagia after pneumonia. Eur Geriatr Med. 2019;10:603–7. https://doi.org/10.1007/s41999-019-00169-1.
10. Kim SJ, Lee JH, Han B, Lam J, Bukowy E, Rao A, et al. Effects of hospital-based physical therapy on hospital discharge outcomes among hospitalized older adults with community-acquired pneumonia and declining physical function. Aging Dis. 2015;6:174–9. https://doi.org/10.14336/AD.2014.0801.
11. Momosaki R, Yasunaga H, Matsui H, Horiguchi H, Fushimi K, Abo M. Effect of early rehabilitation by physical therapists on in-hospital mortality after aspiration pneumonia in the elderly. Arch Phys Med Rehabil. 2015;96:205–9. https://doi.org/10.1016/j.apmr.2014.09.014.

12. Komatsu R, Okazaki T, Ebihara S, Kobayashi M, Tsukita Y, Nihei M, et al. Aspiration pneumonia induces muscle atrophy in the respiratory, skeletal, and swallowing systems. J Cachexia Sarcopenia Muscle. 2018;9:643–53. https://doi.org/10.1002/jcsm.12297.
13. Goto R, Watanabe H, Tanaka N, Kanamori T, Yanagi H. Factors associated with recovery of activities of daily living in elderly pneumonia patients. Gen Med. 2015;16:68–75. https://doi.org/10.1589/jpts.28.2763.
14. Brummel NE, Girard TD. Preventing delirium in the intensive care unit. Crit Care Clin. 2013;29:51–65. https://doi.org/10.1016/j.ccc.2012.10.007.
15. Min L, Wang Z, Wei-Jia H, Lu S-Y, Ya-Zhen F. Effect of feeding management on aspiration pneumonia in elderly patients with dysphagia. Chin Nurs Res. 2015;2:40–4. https://doi.org/10.1016/j.cnre.2015.09.004.
16. Nakamura M, Miyauchi N, Momosaki R. Impact of oral health status on oral intake ability prognosis after pneumonia in older patients: a retrospective cohort study. Eur Geriatr Med. 2019;10:899–903. https://doi.org/10.1007/s41999-019-00237-6.

Chapter 19
Nutritional Care for Aspiration Pneumonia: Can a Nutritional Approach Change the Clinical Course of Aspiration Pneumonia?

Keisuke Maeda

Abstract Nutritional therapy, in addition to antimicrobial therapy, is a promising treatment strategy for patients with aspiration pneumonia. These patients are likely to be aged and malnourished. It is easily conceivable that lack of nutrition during the treatment worsens the malnourishment leading to poor outcomes. However, excessive nutritional administration should also be avoided in the early phase of the disease. Based on the concept of permissive undernutrition, nutrition should be initiated at 50% of the target nutritional goal (30 kcal/kg/day) and gradually increased per week. Moreover, in order to prevent the refeeding syndrome, immediate nutritional screening is necessary at the time of hospitalization. Oral consumption increases nutritional intake. However, nutritional therapy for the older and frail patients should not only achieve the nutritional goal but also include a comprehensive approach associated with oral intake and nutrition. The KT (Kuchi-kara Taberu) index for facilitating oral intake, comprehensive geriatric assessment for abstracting problems, and rehabilitation nutrition for improving physical activity are reliable tools and concepts for a multimodal nutritional approach in patients with aspiration pneumonia.

Keywords Oral feeding · Sarcopenia · Dysphagia · Comprehensive assessment

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1 Introduction

Aspiration pneumonia is defined as pneumonia caused due to the aspiration of bacteria originating in the oral cavity, pharynx, esophagus, or stomach. The main therapeutic strategy for aspiration pneumonia is the use of antibacterial agents related to the specific etiology. Clinicians, therefore, refer to published expert opinions regarding the selection of antibacterial agents and their use. While discussions on drug selection and use are intensifying, no other therapeutic options have yet been fully validated. Aspiration pneumonia is known to be mostly associated with old age [1] and age-related nutritional disorders [2]. Nutritional intervention may, therefore, be important for the prevention of aspiration pneumonia. However, few studies have focused on the relationship between aspiration pneumonia and nutritional therapy. This chapter discusses the possibility that nutritional therapy can contribute to the favorable prognosis of aspiration pneumonia and presents some important concepts of the nutritional approach.

2 Nothing by Mouth During Treatment

Since aspiration pneumonia is a respiratory disease caused by the inhalation of bacteria, any oral intake is often prohibited to avoid further aspiration. However, the prohibition of oral intake has several adverse effects, as shown in Table 19.1. First, the oral hygiene deteriorates during the "nothing by mouth" period. Oral hygiene is maintained not by teeth brushing alone but also depends on the various beneficial effects of saliva. Multidrug-resistant bacteria have been detected in the oral cavity of patients with restricted oral intake [3]. This may be due to the reduced antibacterial and mucosal wetting effects of saliva. In addition, the absence of salivary lubrication also leads to deterioration in the clearance of the oropharynx and oral cavity [4], which results in an increase in the bacterial count and the chance of its aspiration into the lungs. Therefore, restricting oral intake of food may increase the risk of subsequent respiratory infections [5]. Second is the concern that the priority for assessment of oral hygiene and provision for oral care during the "nothing by mouth" period might decline. Although many nurses recognize the need to maintain oral hygiene and care for it, it is usually not a high priority for various reasons [6].

Table 19.1 Unfavorable outcomes of "nothing by mouth" strategy

1.	Poor oral hygiene
2.	Low priority for oral and eating care
3.	Reduced amount of nutritional intake
4.	Decrease in the movement of muscles related to eating
5.	Sarcopenic dysphagia

Although prohibiting oral intake helps in avoiding choking, it can lead to deconditioning of eating-related functions and thereby result in poor outcomes

Nothing by mouth during treatment for aspiration pneumonia can lead to a decrease in the total nutrient intake. In our study of 331 older adult patients with aspiration pneumonia, those who consumed "nothing by mouth" lacked over 3000 kcal of nutrition in the first 5 days [7]. Their daily nutrient intake was significantly lower every day until the seventh day of hospitalization when compared to patients who were allowed oral consumption during the same period. The study also found that inadequate nutrition during the treatment for aspiration pneumonia was associated with the number of days of treatment [7].

"Nothing by mouth" results in a decrease in the movement of muscles associated with swallowing. When compared to normal adults, older adults requiring nursing care show a lower frequency of swallowing during non-meal situations [8]. Inadequate nutritional intake and decreased activity of muscles are known to be involved in the development of sarcopenia [9]. Sarcopenia generally refers to systemic skeletal muscle loss and weakness. In the recent years, the decline in the function of muscles associated with swallowing along with advanced sarcopenia in the whole body has been gathering attention in the field of geriatric nutrition and is referred to as sarcopenic dysphagia [10]. A study found that approximately 40% of the patients who were forced not to take food orally at the start of aspiration pneumonia treatment showed a further decline in their ability to swallow [11]. Considering that many patients with aspiration pneumonia are old and likely to have sarcopenia, the further decrease in their ability to swallow can be attributed mostly to sarcopenic dysphagia. The "nothing by mouth" strategy during treatment for aspiration pneumonia may, therefore, aggravate the condition caused by poor oral hygiene, nutritional deficiencies, and reduced ability to swallow.

3 Individualized Nutritional Support

Nutritional therapy for the treatment of acute diseases is based on personalized and multidisciplinary nutritional support. A randomized controlled trial conducted in acute hospitals, which included 2088 inpatients who were at risk of malnutrition based on an initial nutritional screening performed immediately after hospitalization, demonstrated that multidisciplinary and individualized nutrition therapy was beneficial for the patients [12]. The study included patients with a variety of acute illnesses, and therefore, its conclusions are not limited to those with aspiration pneumonia. However, it can be concluded in general that nutritional therapy during hospitalization is important for patient outcomes. The nutritional screening tools used in clinical settings should be verified for reliability and validity. In hospitalized patients, a preexisting risk of malnutrition detected during the screening upon admission is indicative that malnutrition could become more serious unless adequate nutritional support is not provided. Therefore, it is important to provide personalized nutritional support rather than uniform nutritional therapy to these patients. As for the older adult patients, the individualized nutritional approach is comparable to the comprehensive geriatric assessment [13], which comprehensively evaluates

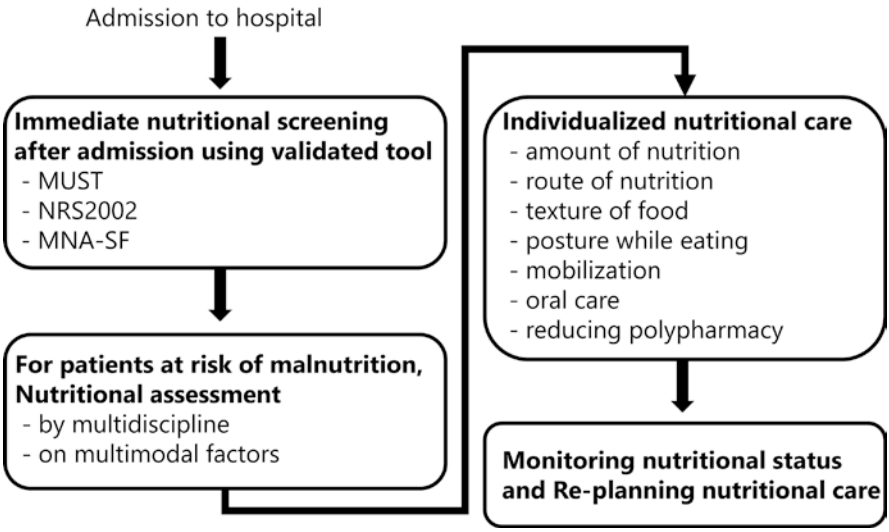

Fig. 19.1 Optimized nutritional care for hospitalized patients. At the time of admission to the hospital, if the patient is at risk of malnutrition, nutritional screening should be performed immediately. Based on the assessment, individualized nutritional care, including safe oral intake, would be provided

various aspects such as the disease, pharmacology, as well as cognitive and physical functions while providing personalized geriatric care. Patients should be screened for malnutrition, assessed multimodally, and provided nutrition based on their individual characteristics, rather than treat all the patients in the same way by prohibiting oral intake or administering nutrition via an enteral tube or a central venous catheter. Considering that the patients with aspiration pneumonia are old and often malnourished, it is reasonable to administer nutrition therapy based on the concept of personalized, multidisciplinary nutrition support (Fig. 19.1). These patients not only have problems with swallowing but are also likely to have physical and cognitive problems [14]. Therefore, as a part of the individualized nutritional approach, care for the physical and cognitive problems is also necessary, along with providing nutrition.

4 Avoiding Refeeding Syndrome

Refeeding syndrome is a highly fatal metabolic complication caused by rapid renutrition in patients with severe undernutrition, starvation, and malnutrition [15]. Under conditions of severe lack of nutrition, rapid administration of nutrition leads to a quick change in the main substrate of energy metabolism from fat to carbohydrate. The resultant glucose load enhances insulin release and stimulates glycogen, fat, and protein synthesis. Insulin also facilitates the absorption of potassium into

the cells. In addition, magnesium and phosphate are also taken up by cells. Changes in osmotic pressure lead to water penetration into the cells, eventually leading to abnormal electrolyte migration and decreased serum levels, 2–5 days after re-nutrition. As a result, refeeding syndrome leads to high mortality following a deterioration in the respiratory and circulation systems [16].

Patients with aspiration pneumonia are likely to be malnourished [17], and older adult patients often have decreased appetite even before admission [18]. The risk of the refeeding syndrome is very high in these conditions, which is further increased if the patient is not allowed oral intake after hospitalization and is instead given parenteral infusion with insufficient nutrition. In order to avoid this risk during hospitalization, it is important to initiate nutritional support immediately after hospitalization. As per the guidelines from the National Institute for Health and Care Excellence [19], patients with any of the following conditions are at a high risk of developing the refeeding syndrome: (1) body mass index <16 kg/m^2, (2) unintentional weight loss of >15% in 3–6 months, (3) little or no nutritional intake for >10 days, and (4) low levels of potassium, phosphate, or magnesium prior to feeding. Additionally, patients who meet two or more of the followings criteria are also considered at a high risk of developing the refeeding syndrome: (1) body mass index <18.5 kg/m^2, (2) unintentional weight loss of >10% in 3–6 months, (3) little or no nutritional intake lasting for >5 days, and (4) a history of alcohol abuse or drugs including insulin, chemotherapy, antacids, or diuretics. Patients with aspiration pneumonia should, therefore, be assessed for the risk of refeeding syndrome as a part of the nutritional screening immediately after hospitalization.

If a risk of the refeeding syndrome is detected, it is recommended that attention be paid to the nutritional content given and the rate of its administration. Starting at 10 kcal/kg/day for the first nutrition dose, it should be gradually increased over a week so that the target nutrition level is achieved in about 7 days. If a body mass index of <14 kg/m^2 or inadequate nutritional intake for more than 15 days is detected, it is better to start the nutritional administration with 5 kcal/kg/day. Patients at risk of refeeding syndrome have depleted thiamin stores in their bodies. Thiamin is known as one of the essential coenzymes needed to produce adenosine triphosphate, which is the main source of energy. Administrating a large dose of thiamin (200–300 mg/day) along with the daily dose of multivitamins and trace elements is, therefore, important when treating patients who are at risk of developing the refeeding syndrome. It is also important to administer nutritional therapy from the first day of hospitalization to prevent the progression of the refeeding syndrome (Fig. 19.2).

5 Amount of Nutrition

It is difficult to specify the exact number of calories that should be administered to patients with aspiration pneumonia. Ideally, an indirect calorimeter should be used to calculate the resting energy expenditure (REE) and multiply it by the activity

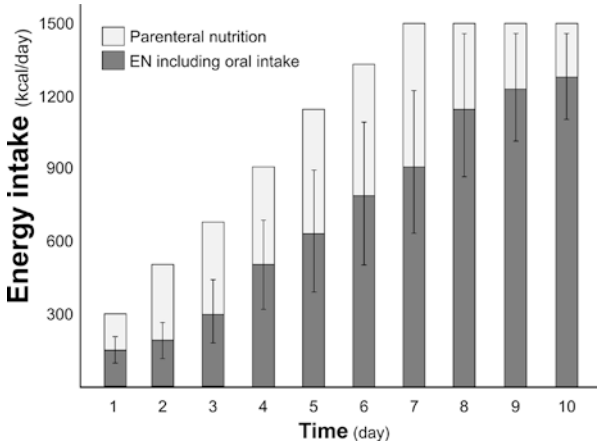

Fig. 19.2 Ideal amount and route of nutritional intake. The concept of permissive undernutrition is recommended for critically ill patients. Nutrition for the first 3 days should not exceed 70% of the final nutritional goal, although excessive lack of nutrition (<50% of the nutritional goal) should also be avoided. The final goal should be met in a week. Oral intake is important to achieve the nutritional and therapeutic goals and to refrain from tube feeding or total parenteral nutrition

factor based on the patient's activity level to estimate the total energy expenditure (TEE). However, personnel-, time-, and cost-related restrictions in clinical practice make using an indirect calorimeter difficult. Therefore, in daily clinical practice, it is recommended that a nutritional dose be set based on an estimation formula.

There are two popular methods for estimating the nutritional dose in a clinical setting. The first is based on Long's formula [20]. After estimating the basal energy expenditure using height, weight, age, and gender (mostly calculated using the Harris-Benedict equation), the TEE is calculated by multiplying the activity coefficient and stress coefficient. The activity coefficient is set to 1.1 or 1.2 depending on the patient's level of activity. It is assumed that the stress coefficient in patients with aspiration pneumonia is affected by the degree of dyspnea, inflammation, and fever. Based on the severity of pneumonia, the stress coefficient can range from 1.2 to 1.5. The other option is to estimate the nutritional dose by simply multiplying the weight by a single coefficient, which ranges from 25 to 35. More practically, an initial nutritional dose that is equal to the patient's weight [kg] x 30 kcal/day is acceptable. With either method, in order to maintain a good nutritional status, the nutritional dose should be estimated based on the actual body weight. If clinicians would like to improve the nutritional status of malnourished patients, the ideal body weight (body weight for body mass index = 22 kg/m^2) should be used for nutritional dose estimation.

The initial nutritional dose for critically ill patients should be set conservatively [21]. Under conditions of high inflammation, energy is also generated endogenously, and therefore, administration of a high dose of nutrition could possibly lead to overnutrition [22]. Although not limited to aspiration pneumonia, overfeeding in critically ill patients is associated with negative outcomes [21]. It is, therefore,

recommended not to exceed 70% of the required nutrition for 3 days after starting the nutritional administration. Ideally, the target nutritional dose should be reached in 5–7 days (Fig. 19.2). The first week of hospitalization is a period of "permissive undernutrition." However, excessive undernutrition and the consequent negative energy balance in critically ill patients also increase the risk of complications. Hence, excessive nutritional deficiencies should be avoided [23]. The initial nutritional dose should be around 50% of the target dose, which should then be gradually increased.

6 Sarcopenia and Aspiration Pneumonia

Sarcopenia is a nutritional disorder that should be considered during the treatment of aspiration pneumonia in older adults. We have previously reported that a decrease in skeletal muscle mass, which is indicative of poor nutritional status [24, 25], detected at hospitalization was associated with increased mortality in patients with aspiration pneumonia [26]. It is also accompanied by a decrease in the mass of muscles involved in respiration and swallowing. Hospitalization can also cause iatrogenic-induced sarcopenia [9]. Therefore, in patients with aspiration pneumonia who often have reduced muscle mass, sarcopenia may worsen with treatment. Computed tomography using the Th12 level of slicing has shown that the muscles of the back are 15% smaller in patients after treatment for aspiration pneumonia when compared to before treatment [27]. In a mouse model of experimental aspiration pneumonia, atrophy of the tongue muscle fiber was observed following the onset of the disease [27]. Loss of muscles associated with respiration and swallowing could be a direct result of inflammation. In addition, sarcopenia caused by a lack of nutrition and low activity during hospitalization is thought to make the situation worse. In patients with aspiration pneumonia, there is a very high risk of further deterioration in the muscles involved in respiration and swallowing. Therefore, in patients with aspiration pneumonia combined with sarcopenia, nutritional care (anti-sarcopenia care) should be strengthened to stop the progression of sarcopenia.

Nutrition therapy for sarcopenia requires multimodal intervention. No interventional trials for sarcopenia in patients with aspiration pneumonia have yet been performed. However, based on the recently published clinical practice guidelines for sarcopenia, nutritional therapy enhanced with essential amino acids and exercise intervention are expected to improve sarcopenia [28]. While it may not be necessary to improve sarcopenia while treating aspiration pneumonia, its further deterioration should be prevented. It is recommended that nutritional therapy should include supplemental parenteral nutrition containing a high dose of essential amino acids or branched-chain amino acids when the oral intake is inadequate or is prohibited. It is highly valuable to administer amino acids for muscle protein catabolism associated with acute inflammatory diseases. An amino acid or protein dose of 1.2 to 1.5 g/kg/day is ideal. A study to evaluate the effectiveness of nutrition therapy to treat sarcopenia in patients with aspiration pneumonia is expected in the future.

7 Transcutaneous Electrical Sensory Stimulation (TESS)

While there is no high-quality evidence supporting nutritional therapeutic strategies for aspiration pneumonia, some of the current strategies have the potential to be beneficial.

TESS is an electrical sensory stimulation therapy delivered through the neck skin. It has recently begun to attract attention in the area of dysphagia rehabilitation. Using an interferential current wave or pulse wave, electrodes applied to the neck skin energize at a threshold without muscle contraction, and the electrical stimulation aims to stimulate the sensory nerve. Patients with dysphagia or aspiration pneumonia often have reduced airway defense sensation thresholds [29]. TESS aims at improving the sensory threshold to reduce aspiration and improve the swallowing function. In a randomized controlled trial, we found that TESS with interferential current wave improved the cough reflex sensitivity and increased the oral nutritional intake [30]. TESS, therefore, has the potential to be beneficial for patients with aspiration pneumonia.

8 Comprehensive Care for Oral Feeding

Oral intake of food is the most important measure to improve nutritional status. When oral intake is prohibited in patients with aspiration pneumonia, the nutritional intake is clearly reduced [7]. However, encouraging oral intake in such patients who are at a high risk of aspiration requires managing the risk of choking. To minimize the risk of aspiration and choking on food, attention should be paid to meal time care such as oral hygiene, eating posture, and adjustment of food texture, as well as non-meal time care such as activities of daily living and physical functions [31]. Therefore, multifaceted and multidisciplinary care should be emphasized in conjunction with nutrition therapy [32].

The Kuchi-kara Taberu (KT) index is suitable for organizing information and assessing conditions related to oral intake in individuals with eating problems (Fig. 19.3). The KT index consists of 13 different multifaceted items that can be

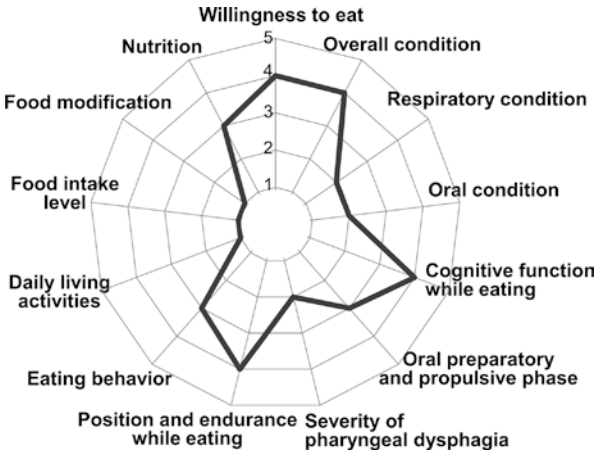

Fig. 19.3 KT index as a facilitation tool for safe eating. KT index developed to facilitate safe oral intake is composed of 13 various aspects related to conditions of eating. When each item is drawn in a radar chart, every medical staff can easily recognize the patient's strengths and weaknesses while eating. This helps in planning individualized nutritional care

used by multidisciplinary teams by visualizing the score on a radar chart. It can also be considered as an individualized nutrition therapy tool to support eating by mouth. The reliability and validity of the KT index have been verified [31], and its use in older patients undergoing rehabilitation has been found to increase the nutritional intake and improve physical functions [33].

9 Rehabilitation Nutrition

A new concept called rehabilitation nutrition has been proposed for nutritional therapy. It promotes living functions such as daily activities and social participation of people with diseases and disabilities [34]. In rehabilitation nutrition, the emphasis is placed on a comprehensive evaluation of life functions, nutritional status, diagnosis, planning, and implementation of individualized nutrition and its regular monitoring. Nutrition therapy should take into consideration the patient's activities, social participation, dietary habits, environmental factors, and medical factors before the onset of aspiration pneumonia. It is clear that nutritional support for the disabled or elderly and frail individuals is not just about administering nutrition. Using multifaceted assessment tools to identify the problems related to nutrition from multiple angles such as the International Classification of Functioning, Disability, and Health, comprehensive geriatric assessment, and the KT index is the first step in initiating rehabilitation nutrition.

10 Conclusions

Nutritional therapy is beneficial for patients with aspiration pneumonia. However, instead of using a standard therapeutic strategy, clinicians should perform an immediate and comprehensive assessment to provide individualized nutritional care, because these patients are most likely to be old and frail with comorbidities and eating problems.

References

1. Teramoto S, Fukuchi Y, Sasaki H, Sato K, Sekizawa K, Matsuse T, et al. High incidence of aspiration pneumonia in community- and hospital-acquired pneumonia in hospitalized patients: a multicenter, prospective study in Japan. J Am Geriatr Soc. 2008;56(3):577–9. https://doi.org/10.1111/j.1532-5415.2008.01597.x.
2. van der Maarel-Wierink CD, Vanobbergen JN, Bronkhorst EM, Schols JM, de Baat C. Risk factors for aspiration pneumonia in frail older people: a systematic literature review. J Am Med Dir Assoc. 2011;12(5):344–54. https://doi.org/10.1016/j.jamda.2010.12.099.
3. Leibovitz A, Plotnikov G, Habot B, Rosenberg M, Segal R. Pathogenic colonization of oral flora in frail elderly patients fed by nasogastric tube or percutaneous enterogastric tube. J Gerontol A Biol Sci Med Sci. 2003;58(1):52–5. https://doi.org/10.1093/gerona/58.1.m52.

4. Palmer LB, Albulak K, Fields S, Filkin AM, Simon S, Smaldone GC. Oral clearance and pathogenic oropharyngeal colonization in the elderly. Am J Respir Crit Care Med. 2001;164(3):464–8. https://doi.org/10.1164/ajrccm.164.3.2008149.
5. Brogan E, Langdon C, Brookes K, Budgeon C, Blacker D. Can't swallow, can't transfer, can't toilet: factors predicting infections in the first week post stroke. J Clin Neurosci. 2015;22(1):92–7. https://doi.org/10.1016/j.jocn.2014.05.035.
6. Costello T, Coyne I. Nurses' knowledge of mouth care practices. Br J Nurs. 2008;17(4):264–8. https://doi.org/10.12968/bjon.2008.17.4.28716.
7. Maeda K, Koga T, Akagi J. Tentative nil per os leads to poor outcomes in older adults with aspiration pneumonia. Clin Nutr. 2016;35(5):1147–52. https://doi.org/10.1016/j.clnu.2015.09.011.
8. Tanaka N, Nohara K, Kotani Y, Matsumura M, Sakai T. Swallowing frequency in elderly people during daily life. J Oral Rehabil. 2013;40(10):744–50. https://doi.org/10.1111/joor.12085.
9. Cruz-Jentoft AJ, Sayer AA. Sarcopenia. Lancet. 2019;393(10191):2636–46. https://doi.org/10.1016/S0140-6736(19)31138-9.
10. Clave P, Shaker R. Dysphagia: current reality and scope of the problem. Nat Rev Gastroenterol Hepatol. 2015;12(5):259–70. https://doi.org/10.1038/nrgastro.2015.49.
11. Momosaki R, Yasunaga H, Matsui H, Horiguchi H, Fushimi K, Abo M. Predictive factors for oral intake after aspiration pneumonia in older adults. Geriatr Gerontol Int. 2016;16(5):556–60. https://doi.org/10.1111/ggi.12506.
12. Schuetz P, Fehr R, Baechli V, Geiser M, Deiss M, Gomes F, et al. Individualised nutritional support in medical inpatients at nutritional risk: a randomised clinical trial. Lancet. 2019;393(10188):2312–21. https://doi.org/10.1016/S0140-6736(18)32776-4.
13. Ellis G, Whitehead MA, O'Neill D, Langhorne P, Robinson D. Comprehensive geriatric assessment for older adults admitted to hospital. Cochrane Database Syst Rev. 2011;7:CD006211. https://doi.org/10.1002/14651858.CD006211.pub2.
14. Maeda K, Wakabayashi H, Shamoto H, Akagi J. Cognitive impairment has no impact on hospital-associated dysphagia in aspiration pneumonia patients. Geriatr Gerontol Int. 2018;18(2):233–9. https://doi.org/10.1111/ggi.13164.
15. Skipper A. Refeeding syndrome or refeeding hypophosphatemia: a systematic review of cases. Nutr Clin Pract. 2012;27(1):34–40. https://doi.org/10.1177/0884533611427916.
16. Mehanna HM, Moledina J, Travis J. Refeeding syndrome: what it is, and how to prevent and treat it. BMJ. 2008;336(7659):1495–8. https://doi.org/10.1136/bmj.a301.
17. Kohno S, Imamura Y, Shindo Y, Seki M, Ishida T, Teramoto S, et al. Clinical practice guidelines for nursing- and healthcare-associated pneumonia (NHCAP) [complete translation]. Respir Investig. 2013;51(2):103–26. https://doi.org/10.1016/j.resinv.2012.11.001.
18. Takada T, Yamamoto Y, Terada K, Ohta M, Mikami W, Yokota H, et al. Diagnostic utility of appetite loss in addition to existing prediction models for community-acquired pneumonia in the elderly: a prospective diagnostic study in acute care hospitals in Japan. BMJ Open. 2017;7(11):e019155. https://doi.org/10.1136/bmjopen-2017-019155.
19. Excellence NIfHaC. Nutrition support for adults: oral nutrition support, enteral tube feeding and parenteral nutrition. 2016. https://www.nice.org.uk/guidance/cg32. Accessed Dec 20 2019.
20. Long CL, Schaffel N, Geiger JW, Schiller WR, Blakemore WS. Metabolic response to injury and illness: estimation of energy and protein needs from indirect calorimetry and nitrogen balance. JPEN J Parenter Enteral Nutr. 1979;3(6):452–6. https://doi.org/10.1177/014860717900300609.
21. Singer P, Blaser AR, Berger MM, Alhazzani W, Calder PC, Casaer MP, et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clin Nutr. 2019;38(1):48–79. https://doi.org/10.1016/j.clnu.2018.08.037.
22. Tappy L, Schwarz JM, Schneiter P, Cayeux C, Revelly JP, Fagerquist CK, et al. Effects of isoenergetic glucose-based or lipid-based parenteral nutrition on glucose metabolism, de novo lipogenesis, and respiratory gas exchanges in critically ill patients. Crit Care Med. 1998;26(5):860–7. https://doi.org/10.1097/00003246-199805000-00018.

23. Dvir D, Cohen J, Singer P. Computerized energy balance and complications in critically ill patients: an observational study. Clin Nutr. 2006;25(1):37–44. https://doi.org/10.1016/j.clnu.2005.10.010.
24. Cederholm T, Jensen GL, Correia M, Gonzalez MC, Fukushima R, Higashiguchi T, et al. GLIM criteria for the diagnosis of malnutrition–a consensus report from the global clinical nutrition community. J Cachexia Sarcopenia Muscle. 2019;10(1):207–17. https://doi.org/10.1002/jcsm.12383.
25. Smirnova LP, Krotenko NV, Grishko EV, Krotenko NM, Alifirova VM, Ivanova SA. State of antioxidant system in patients with multiple sclerosis during therapy. Biomed Khim. 2011;57(6):661–70. https://doi.org/10.18097/pbmc20115706661.
26. Maeda K, Akagi J. Muscle mass loss is a potential predictor of 90-day mortality in older adults with aspiration pneumonia. J Am Geriatr Soc. 2017;65(1):e18–22. https://doi.org/10.1111/jgs.14543.
27. Komatsu R, Okazaki T, Ebihara S, Kobayashi M, Tsukita Y, Nihei M, et al. Aspiration pneumonia induces muscle atrophy in the respiratory, skeletal, and swallowing systems. J Cachexia Sarcopenia Muscle. 2018;9(4):643–53. https://doi.org/10.1002/jcsm.12297.
28. Arai H, Wakabayashi H, Yoshimura Y, Yamada M, Kim H, Harada A. Chapter 4 treatment of sarcopenia. Geriatr Gerontol Int. 2018;18(Suppl 1):28–44. https://doi.org/10.1111/ggi.13322.
29. Nakashima T, Maeda K, Tahira K, Taniguchi K, Mori K, Kiyomiya H, et al. Silent aspiration predicts mortality in older adults with aspiration pneumonia admitted to acute hospitals. Geriatr Gerontol Int. 2018;18(6):828–32. https://doi.org/10.1111/ggi.13250.
30. Maeda K, Koga T, Akagi J. Interferential current sensory stimulation, through the neck skin, improves airway defense and oral nutrition intake in patients with dysphagia: a double-blind randomized controlled trial. Clin Interv Aging. 2017;12:1879–86. https://doi.org/10.2147/CIA.S140746.
31. Maeda K, Shamoto H, Wakabayashi H, Enomoto J, Takeichi M, Koyama T. Reliability and validity of a simplified comprehensive assessment tool for feeding support: Kuchi-Kara Taberu index. J Am Geriatr Soc. 2016;64(12):e248–e52. https://doi.org/10.1111/jgs.14508.
32. Koyama T, Shamoto H, Anzai H, Koganei Y, Maeda K, Wakabayashi H. Multidisciplinary Comprehensive Care for Early Recommencement of Oral intake in older adults with severe pneumonia. J Gerontol Nurs. 2016;42(10):21–9. https://doi.org/10.3928/00989134-20160913-05.
33. Waza M, Maeda K, Katsuragawa C, Sugita A, Tanaka R, Ohtsuka A, et al. Comprehensive tool to assess Oral feeding support for functional recovery in post-acute rehabilitation. J Am Med Dir Assoc. 2019;20(4):426–31. https://doi.org/10.1016/j.jamda.2018.10.022.
34. Wakabayashi H. Rehabilitation nutrition in general and family medicine. J Gen Fam Med. 2017;18(4):153–4. https://doi.org/10.1002/jgf2.116.

Chapter 20
Surgical Approach: The Indication and Efficacy of Surgical Therapy for Aspiration Pneumonia

Masamitsu Hyodo, Asuka Nagao, and Kahori Hirose

Abstract The incidence of dysphagia is increasing, particularly among the elderly. Patients with severe dysphagia are unable to take food orally and also face the life-threatening condition of aspiration pneumonia. Therefore, treatment for a swallowing disorder is focused on restoring oral intake and preventing aspiration pneumonia. In cases of very severe dysphagia and in patients with progressive disease, surgical intervention is an alternative option to restore oral feeding and prevent recurrent aspiration pneumonia. Surgeries to restore swallowing function aim to address impaired pharyngolaryngeal function during the pharyngeal swallowing stage. These surgeries are indicated for patients with severely impaired pharyngeal swallowing. The oral and esophageal swallowing functions should also be maintained. The procedures used to this end include laryngeal suspension, cricopharyngeal myotomy, and vocal cord medialization. In contrast, aspiration-prevention surgery is designed to preclude the possibility of aspiration pneumonia completely, by separating the lower respiratory tract from the pharynx and larynx in cases of intractable dysphagia. Although this operation sacrifices laryngeal function, it has recently attracted attention as a method to avoid infection of the lower respiratory tract due to aspiration. Procedures including total laryngectomy, laryngotracheal separation, and laryngeal closure not only prevent aspiration pneumonia but also improve patient quality of life.

Keywords Pharyngeal swallowing stage · Laryngeal suspension · Cricopharyngeal myotomy · Laryngotracheal separation

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1 Introduction

With our aging society, swallowing disorders due to cerebrovascular disorders or neuromuscular diseases have become a major issue in medicine and society [1]. Patients with severe dysphagia are not only unable to take foods orally but also face life-threatening problems due to aspiration pneumonia, especially in the elderly population. In Japan, pneumonia has become the third most common cause of death [2]. The majority of pneumonia cases among the elderly is associated with swallowing disorders. Therefore, the goal of the treatment of swallowing disorders should be to recover oral intake and prevent aspiration pneumonia. The treatments for dysphagia include modifying food properties, oral care procedures, pharmacological therapy, and swallowing rehabilitation [3]. However, patients with very severe dysphagia or those with progressive disease cannot achieve sufficient improvement. In these cases, surgical intervention is an option for restoring oral feeding and preventing recurrent aspiration pneumonia [4]. This chapter outlines the surgical treatments for swallowing disorders and describes their roles.

2 Classification of the Surgical Treatment for Dysphagia

The surgical treatment of dysphagia is classified into procedures to improve swallowing function and those to prevent aspiration while swallowing. The former restores oral feeding, while preserving the laryngeal function represented by phonation and physiological respiration. In comparison, aspiration-prevention surgery is aimed at preventing the occurrence of aspiration pneumonia even at the expense of voice function. It is indicated for patients with severely impaired or progressive dysphagia presenting with repeated lower airway infections. Both types include several surgical procedures, and the indications for these procedures, and their surgical techniques, are outlined below.

3 Surgery to Improve Swallowing Function

Swallowing movements consist of the oral preparatory, oral, pharyngeal, and esophageal stages. The oral preparatory and oral stages involve voluntary muscle action to take food into the mouth, masticate it, mix it with saliva, divide it to suitable sizes for deglutition, and transport it into the pharynx. The pharyngeal stage consists of complex reflexive movements of the swallowing organs, including nasopharyngeal closure, tongue elevation, glottal closure, laryngeal elevation, pharyngeal contraction, and opening of the upper esophageal sphincter (UES) [5]. The esophageal stage consists of peristaltic movements to drive food into the stomach. Of these stages, the pharyngeal stage is the most complex and precise

and can vary by cause. When impaired, patients suffer from frequent, recurrent aspiration resulting in intractable pneumonia.

Surgery to restore swallowing function is aimed at compensating for or strengthening impaired pharyngolaryngeal functions in the pharyngeal swallowing stage. These surgical procedures include pharyngeal valvuloplasty, laryngeal suspension, infrahyoid myotomy, vocal cord medialization (medialization thyroplasty, arytenoid adduction, injection augmentation), pharyngeal constriction, and cricopharyngeal myotomy (Fig. 20.1). Table 20.1 shows the indications for each procedure. Of these procedures, laryngeal suspension, cricopharyngeal myotomy, and vocal cord medialization are frequently used and have important roles in the restoration of oral food intake.

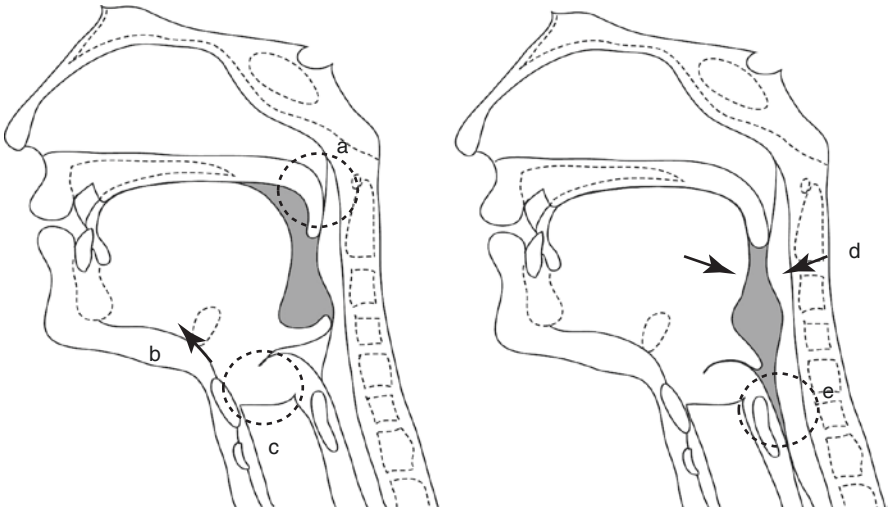

Fig. 20.1 Surgeries to improve swallowing function. (**a**) Pharyngeal valvuloplasty, (**b**) laryngeal suspension with infrahyoid myotomy, (**c**) vocal cord medialization, (**d**) pharyngeal constriction, (**e**) cricopharyngeal myotomy

Table 20.1 Surgical procedures to improve swallowing function

Surgical procedure	Indication
Pharyngeal valvuloplasty	Insufficient nasopharyngeal closure
Laryngeal suspension Infrahyoid myotomy	Insufficient or delayed laryngeal elevation
Medialization thyroplasty Arytenoid adduction Injection augmentation of the vocal cords	Unilateral vocal cord paralysis Vocal cord atrophy
Pharyngeal constriction	Pharyngeal paralysis
Cricopharyngeal myotomy	Insufficient opening of the upper esophageal sphincter

3.1 Surgical Indications

As mentioned above, surgery to improve swallowing function is aimed at compensating for impaired pharyngolaryngeal movements. Therefore, it is indicated for patients in whom the pharyngeal swallowing stage is chiefly impaired. Cases presenting with severely disturbed oral or esophageal swallowing stages are not candidates. Additional indication criteria include (1) maintained swallowing reflex initiation, (2) insufficient structured swallowing rehabilitation, (3) stable underlying disease, (4) patient's strong desire for oral food intake, and (5) sufficient consciousness level, cognitive function, and activities of daily living (ADL) to undergo postoperative swallowing rehabilitation. The age of the patient is another important factor. Patients older than 75 years are not suitable for this surgery.

3.2 Laryngeal Suspension

Anterosuperior movement of the larynx is essential during the pharyngeal swallowing phase for laryngeal closure and passive opening of the esophageal entrance. Therefore, laryngeal suspension is indicated for cases with insufficient or delayed laryngeal elevation. The preoperative evaluation requires videofluorographic examination to assess the surgical indications. Although there are several surgical methods, we frequently use thyroid cartilage proximation and fixation to the anterior part of the mandible to obtain sufficient laryngeal elevation (Fig. 20.2). We use Teflon tape to fix the thyroid cartilage during the surgery, as it is strong enough to maintain long-term laryngeal suspension. A tracheostomy is required for postoperative airway management due to the temporary laryngopharyngeal mucosal edema. The edema usually disappears within a few weeks. Figure 20.3 shows pre- and postoperative radiographic images. Postoperatively, the larynx is located in an anterosuperior position, and the upper esophageal entrance is wide open in the non-swallowing phase. As a result, aspiration during swallowing decreases, and the food bolus easily passes through the esophageal entrance [4]. The usefulness of laryngeal suspension has been reported on previously, particularly for patients who have undergone extensive head and neck cancer resection [6, 7].

3.3 Cricopharyngeal Myotomy

The cricopharyngeal muscle functions as the UES, while it relaxes during the pharyngeal stage of swallowing to allow the food bolus to pass. Its movement is precisely controlled by the central pattern generator of swallowing in the medulla oblongata. The motor nerve of the muscle is the vagus nerve and cerebrovascular or

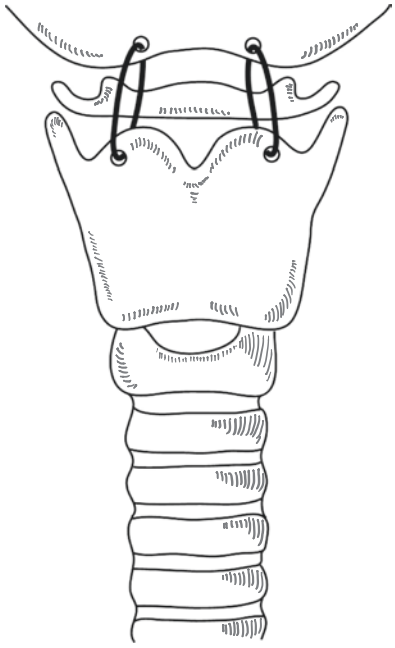

Fig. 20.2 Schema for laryngeal suspension. The thyroid cartilage is suspended toward the mandible and fixed

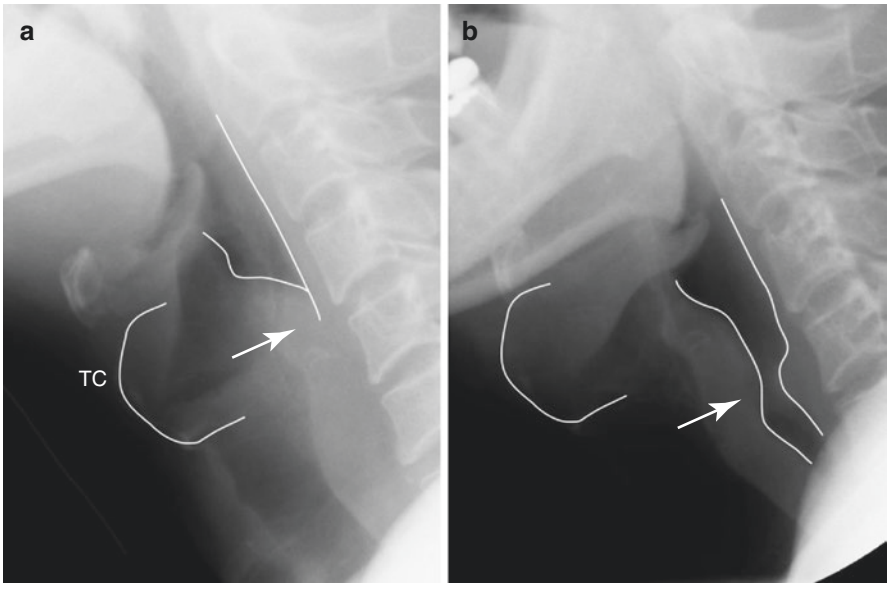

Fig. 20.3 Lateral radiographic images of a patient who underwent laryngeal suspension acquired in the non-swallowing phase. The esophageal entrance is closed preoperatively (**a**) (arrow). Postoperatively (**b**), the thyroid cartilage (TC) is suspended anterosuperiorly, and the upper esophageal entrance is wide open (arrow)

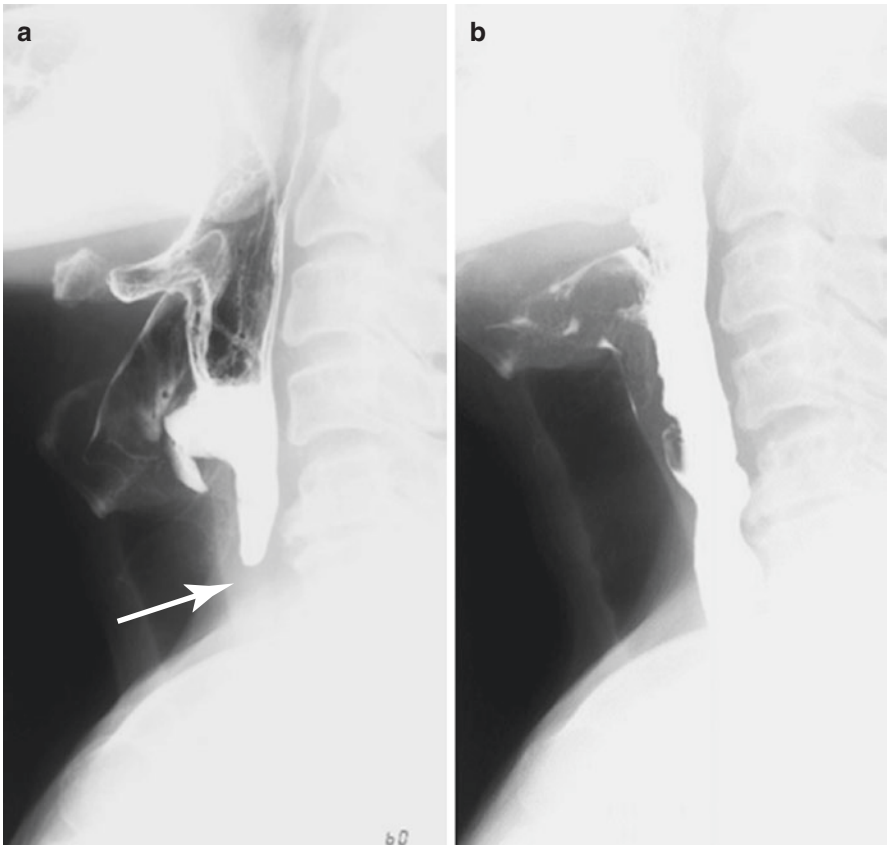

Fig. 20.4 Videofluorographic images of a patient who underwent cricopharyngeal myotomy. Obstruction of the upper esophageal sphincter (arrow) and aspiration of contrast medium are seen preoperatively (**a**). Postoperatively, the contrast medium passes freely and aspiration is minimal (**b**)

neuromuscular diseases can easily cause functional disorders. A cricopharyngeal myotomy facilitates the passage of food through the entrance of the esophagus by sectioning the muscle and is the most representative operation for restoring swallowing function. This procedure was first reported in 1951 by Kaplan [8] for patients with medullary gray leukomyelitis and is now widely applied in dysphagia due to various diseases [9, 10]. The surgical indication is determined by a videofluorographic examination that shows impaired opening of the UES and residual contrast medium in the piriform sinus (Fig. 20.4a).

As shown in Fig. 20.5, the cricopharyngeal muscle is bilaterally "resected" in a 3-cm-long, 1-cm-wide shape to avoid reattachment of the cut end of the muscle. The lower part of the thyropharyngeal muscle and upper part of the esophageal

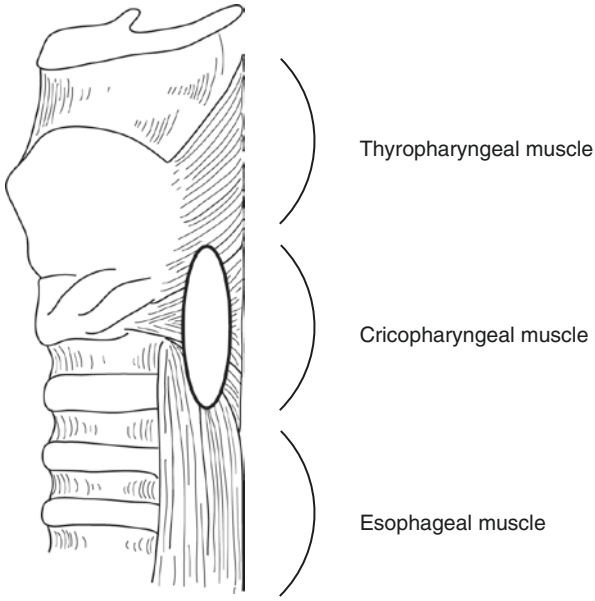

Fig. 20.5 Schema for cricopharyngeal myotomy. The cricopharyngeal muscle is resected as an oval shape

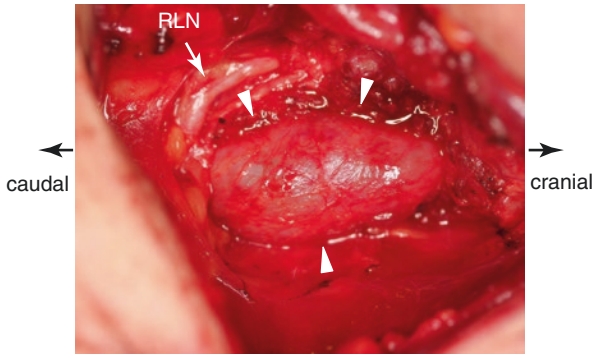

Fig. 20.6 Intraoperative findings of cricopharyngeal myotomy. The pharyngoesophageal mucous membrane bulges following myotomy (arrow head). *RLN* Recurrent laryngeal nerve

muscle are included in the resection. If the muscle fibers are cut completely, the mucous membrane of the esophageal entrance will bulge in synchrony with ventilation (Fig. 20.6). The recurrent laryngeal nerve, which runs antero-caudally, should not be injured. Postoperatively, the passage of the contrast medium is improved, and aspiration is significantly decreased (Fig. 20.4b). As the patients lose UES function postoperatively, it is necessary to consider gastroesophageal reflux.

An endoscopic approach for cricopharyngeal myotomy has been increasingly employed [11, 12]. Huntley et al. [13] compared open and endoscopic cricopharyngeal myotomy and concluded that the endoscopic approach is a safe and effective

alternative to the open approach. In addition, patients undergoing endoscopic cricopharyngeal myotomy have shorter operative times.

3.4 Vocal Cord Medialization

Bulbar paresis, such as Wallenberg syndrome, may present with unilateral vocal cord paralysis. Surgeries for the thyroid gland, skull base, esophagus, and dissecting aortic aneurysm may also result in recurrent laryngeal nerve paralysis. In a patient with vocal cord paralysis, glottal closure during swallowing becomes insufficient, and aspiration is likely. Vocal cord paralysis is accompanied by breathy hoarseness. For such cases, glottal closure during swallowing can be strengthened by surgical medialization of the paralyzed vocal cord. Procedures include medialization thyroplasty [14, 15], arytenoid adduction [16], and injection augmentation of the vocal cords using autologous fat tissue or collagen [17] (Fig. 20.7). Injection augmentation is also effective for treating insufficient glottal closure due to vocal cord atrophy [18]. These procedures lessen aspiration and also improve the breathy voice. Figure 20.8 shows the surgical schema and pre- and postoperative laryngeal findings during sustained phonation.

4 Surgery to Prevent Aspiration Pneumonia

Aspiration-prevention surgery is a procedure that precludes aspiration pneumonia entirely by separating the lower respiratory tract from the pharynx and larynx for patients with intractable dysphagia. Although this operation sacrifices

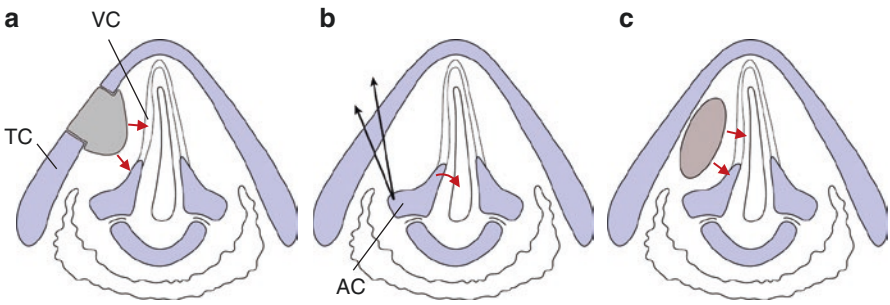

Fig. 20.7 Schema for vocal cord medialization surgeries. (**a**) Medialization thyroplasty (lateral compression of the vocal cord), (**b**) arytenoid adduction, (**c**) injection augmentation of the vocal cord. *VC* vocal cord, *TC* thyroid cartilage, *AC* arytenoid cartilage

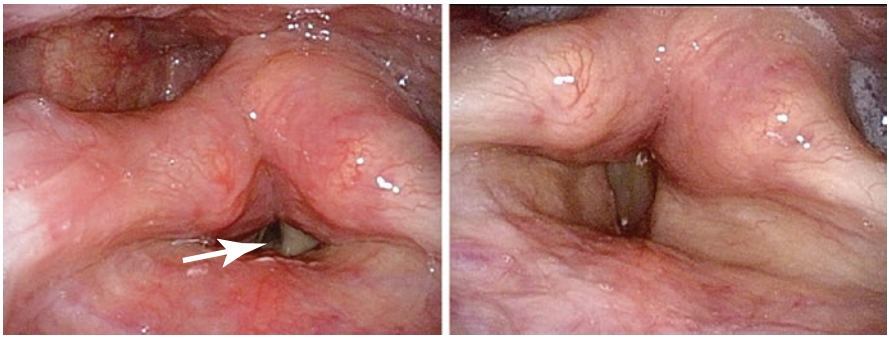

Fig. 20.8 Laryngeal findings in a patient with left vocal cord paralysis. Preoperatively, glottal insufficiency during phonation is obvious (arrow). Sufficient glottal closure is achieved following arytenoid adduction

laryngeal function, it has recently attracted attention as a method to avoid lower respiratory tract infection due to aspiration.

4.1 Surgical Indications

The indications for aspiration-prevention surgery are summarized as follows: (1) severe dysphagia rehabilitation and surgery to improve swallowing function are insufficient; (2) there is a repeated history or high risk of aspiration pneumonia; and (3) the patient and family agree to the loss of phonation.

Although patients lose the ability to communicate verbally postoperatively, those with severe aspiration require tracheal management including tracheostomy. Such patients in this study had impaired voice function preoperatively.

4.2 Surgical Procedures

Several surgical options are available, including total laryngectomy, laryngotracheal separation, and laryngeal closure. Total laryngectomy is relatively invasive, and removal of the larynx is a psychological burden for the patients or their families. Laryngotracheal separation is less invasive, relatively easy to perform, and reliable, particularly in children. Lindeman et al. [19] reported the original procedure to anastomose the cranial stump of the separated trachea to the esophagus (tracheo-esophageal anastomosis) and a modified procedure to make the cranial trachea a dead end (laryngotracheal diversion) (Fig. 20.9). These procedures do not remove

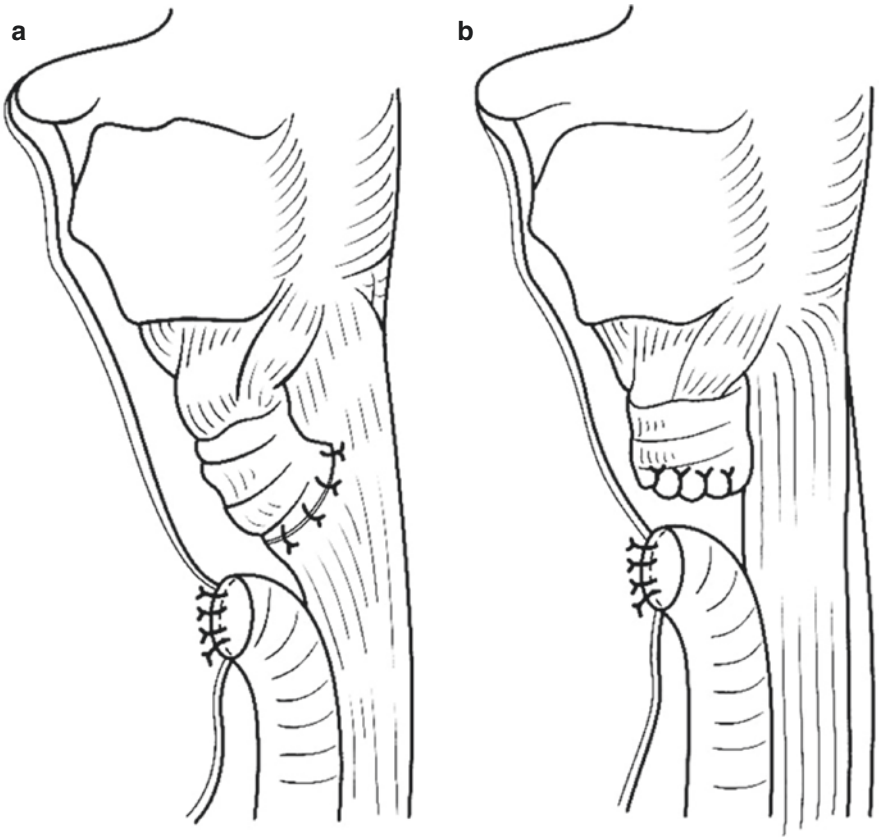

Fig. 20.9 Schema for Lindeman's laryngotracheal separation surgery. (**a**) Cranial stump of the trachea is anastomosed to the esophagus; (**b**) cranial stump of the trachea is closed to create a dead end

or devastate the larynx, which shortens the operating time and lessens the psychological burden [20]. Figure 20.10 shows videofluorographic images after Lindeman's laryngotracheal separation. Laryngeal closure is a simple and minimally invasive procedure [21]. Therefore, it is suitable for patients of various ages.

4.3 Efficacy of the Surgery

Postoperatively, the risk of intractable lower airway infection is eliminated, and the patients may recover oral intake. Moreover, since it minimizes intratracheal suction, the burden on patients, families, and caregivers is reduced remarkably. Therefore, many patients can stay at home safely, leading to improved quality of life (QOL) and a reduced need for hospitalization [20, 22, 23]. Therefore, the impact of this surgery is significant.

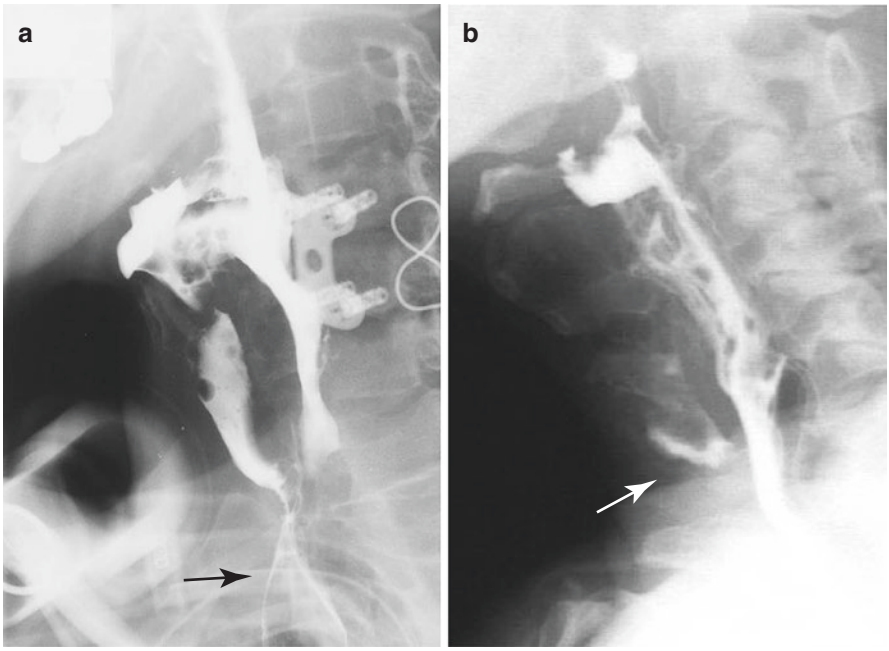

Fig. 20.10 Videofluorographic images following laryngotracheal separation. (**a**) Tracheoesophageal anastomosis, aspirated contrast medium flows into the esophagus. (arrow); (**b**) laryngotracheal diversion, aspirated medium remains in the cut end of the trachea (arrow)

5 Conclusion

The goal of treating dysphagia is to restore oral food intake and prevent intractable aspiration pneumonia. Conservative treatment is a fundamental strategy; however, surgical intervention plays an important role for patients with severe dysphagia. Surgery to improve swallowing function is indicated to compensate for or strengthen impaired pharyngolaryngeal function. Aspiration-prevention surgery avoids recurrent bronchopulmonary infection and is indicated for patients suffering from intractable dysphagia at high risk of aspiration pneumonia. These surgeries can improve the QOL of both patients and their families. Clinicians should consider these surgical options for intractable swallowing disorders.

References

1. Wirth R, Dziewas R, Beck AM, Clavé P, Hamdy S, Heppner HJ, et al. Oropharyngeal dysphagia in older persons–from pathophysiology to adequate intervention: a review and summary of an international expert meeting. Clin Interv Aging. 2016;11:189–208.
2. https://www.mhlw.go.jp/toukei/saikin/hw/jinkou/geppo/nengai18/dl/gaikyou30.pdf.

3. Yamaya M, Yanai M, Ohrui T, Arai H, Sasaki H. Interventions to prevent pneumonia among older adults. J Am Geriatr Soc. 2001;49:85–90.
4. Shin T, Tsuda K, Takagi S. Surgical treatment for dysphagia of neuromuscular origin. Folia Phoniatr Logop. 1999;51:213–9.
5. Bass NH. The neurology of swallowing. In: Groher ME, editor. Dysphagia: diagnosis and management. 3rd ed. Newton: Butterworth-Heinemann; 1997. p. 7–35.
6. Goode RL. Laryngeal suspension in head and neck surgery. Laryngoscope. 1976;86:349–55.
7. Fujimoto Y, Hasegawa Y, Yamada H, Ando A, Nakashima T. Swallowing function following extensive resection of oral or oropharyngeal cancer with laryngeal suspension and cricopharyngeal myotomy. Laryngoscope. 2007;117:1343–8.
8. Kaplan S. Paralysis of deglutition, a post-poliomyelitis complication treated by section of the cricopharyngeus muscle. Ann Surg. 1951;133:572–3.
9. Lindgren S, Ekberg O. Cricopharyngeal myotomy in the treatment of dysphagia. Clin Otolaryngol Allied Sci. 1990;15:221–7.
10. Kelly JH. Management of upper esophageal sphincter disorders: indications and complications of myotomy. Am J Med. 2000;108:43S–6S.
11. Ho AS, Morzaria S, Damrose EJ. Carbon dioxide laser-assisted endoscopic cricopharyngeal myotomy with primary mucosal closure. Ann Otol Rhinol Laryngol. 2011;120:33–9.
12. Chitose S, Sato K, Hamakawa S, Umeno H, Nakashima T. A new paradigm of endoscopic cricopharyngeal myotomy with CO2 laser. Laryngoscope. 2011;121:567–70.
13. Huntley C, Boon M, Spiegel J. Open vs. endoscopic cricopharyngeal myotomy; is there a difference? Am J Otolaryngol. 2017;38(4):405–7.
14. Isshiki N, Okamura H, Ishikawa T. Thyroplasty type I (lateral compression) for dysphonia due to vocal cord paralysis or atrophy. Acta Otolaryngol. 1975;80:465–73.
15. Flint PW, Purcell LL, Cummings CW. Pathophysiology and indications for medialization thyroplasty in patients with dysphagia and aspiration. Otolaryngol Head Neck Surg. 1997;116:349–54.
16. Isshiki N, Tanabe M, Sawada M. Arytenoid adduction for unilateral vocal cord paralysis. Arch Otolaryngol. 1978;104:555–8.
17. Patel NJ, Kerschner JE, Merati AL. The use of injectable collagen in the management of pediatric vocal unilateral fold paralysis. Int J Pediatr Otorhinolaryngol. 2003;67:1355–60.
18. Howell RJ, Webster H, Kissela E, Gustin R, Kaval F, Klaben B, et al. Dysphagia in Parkinson's disease improves with vocal augmentation. Dysphagia. 2019;34(6):862–8. https://doi.org/10.1007/s00455-019-09982-z.
19. Lindeman RC. Diverting the paralyzed larynx: a reversible procedure for intractable aspiration. Laryngoscope. 1975;85:157–80.
20. Shima H, Kitagawa H, Wakisaka M, Furuta S, Hamano S, Aoba T. The usefulness of laryngotracheal separation in the treatment of severe motor and intellectual disabilities. Pediatr Surg Int. 2010;26:1041–4.
21. Takano S, Goto T, Kabeya M, Tayama N. Surgical closure of the larynx for the treatment of intractable aspiration: surgical technique and clinical results. Laryngoscope. 2012;122:1273–8.
22. Shama L, Connor NP, Ciucci MR, McCulloch TM. Surgical treatment of dysphagia. Phys Med Rehabil Clin N Am. 2008;19:817–35.
23. Eisele DW, Yarington CT Jr, Lindeman RC. Indications for the tracheoesophageal diversion procedure and the laryngotracheal separation procedure. Ann Otol Rhinol Laryngol. 1988;97:471–5.

Part IV
Topics of Aspiration Pneumonia

Chapter 21
Emerging the Notion and Definition of NHCAP: What Is the NHCAP? Why Aspiration Pneumonia Is Important in NHCAP?

Masafumi Seki

Abstract Healthcare-associated pneumonia (HCAP) overlapped both community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP), since most cases of HCAP in Japan are diagnosed as "aspiration pneumonia" in the elderly persons who are receiving nursing care. Therefore, a separating category and term are recommended as "nursing- and healthcare-associated pneumonia (NHCAP)." The treatment by antibiotics should be used carefully to prevent the undesired care and antimicrobial resistance, and the care including vaccination and infection control should have priority rather than cure in the management of NHCAP patients, including most aspiration pneumonia patients in Japan.

Keywords Aspiration pneumonia · Antimicrobial resistance · Antimicrobial stewardship · Diagnostic stewardship · Healthcare-associated pneumonia (HCAP) Infection control · Vaccine

1 Introduction: Concept of NHCAP

The mortality rate of pneumonia is 1000 times higher among the elderly 85 years of age and over than among young adults irrespective of gender [1], and pneumonia is the first leading cause of death of males 90 years of age and over in Japan. The Japanese Respiratory Society published guidelines for the management of

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community-acquired pneumonia (CAP) in 2000 and guidelines for the management of hospital-acquired pneumonia (HAP) in 2002 (revised edition published in 2007 and 2008, respectively) [2, 3] with the aim of supporting the management of pneumonia, whose morbidity and mortality rates in the elderly are high.

However, these earlier guidelines did not always play an adequate role as standards for clinical practice in regard to elderly patients, who have a high morbidity rate, because elderly pneumonia patients may be classified as having both CAP and HAP due to the fact that they are often admitted to healthcare-related facilities, such as nursing homes, that are intermediate between hospitals and communities and because the outcome of pneumonia in the elderly population is worse than its outcome in the younger population.

The issues related to the handling of HAP and CAP are not limited to Japan. The American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) made recommendations in regard to the treatment of such conditions as healthcare-associated pneumonia (HCAP) in the HAP guidelines [4] that they published jointly in 2005. However, the meaning of "HC" (healthcare) in the guidelines jointly published by the ATS and IDSA is not always the same as in Japan; the Japanese healthcare system is characterized by universal nursing care insurance for those 65 years of age and over and by universal health insurance for the entire population; it is important to create a "Japanese version of HCAP" guidelines that include both nursing care-associated pneumonia and healthcare-associated pneumonia.

2 Clinical Significance of HCAP in the United States and Other Countries

The disease concept HCAP was publicly described for the first time in the HAP guidelines jointly published by the ATS and the IDSA in 2005 [4]. In Japan, it is more appropriate to use the term "NHCAP" instead of HCAP for the reasons stated below.

Internationally the term HCAP is generally used, and initially the HCAP population was defined as a group of CAP patients or HAP patients who had risk factors for involvement by drug-resistant pathogens [4].

However, many reports on HCAP, mainly from the United States (USA), showed that the resistance of the causative agents and outcomes (mortality rates) in HCAP were similar to the resistance of the causative agents and outcomes (mortality rates) in HAP [5]. In their words, it was found that some of the patients who had been admitted to a hospital with an initial diagnosis of CAP were older and had a poorer outcome than CAP patients, and the causative agents isolated from most of them were drug-resistant pathogens (*methicillin-resistant Staphylococcus aureus* (MRSA) and Gram-negative bacteria such as *Pseudomonas aeruginosa*), in addition to the pneumococci and *Haemophilus influenzae* that were the causative agents isolated from CAP patients.

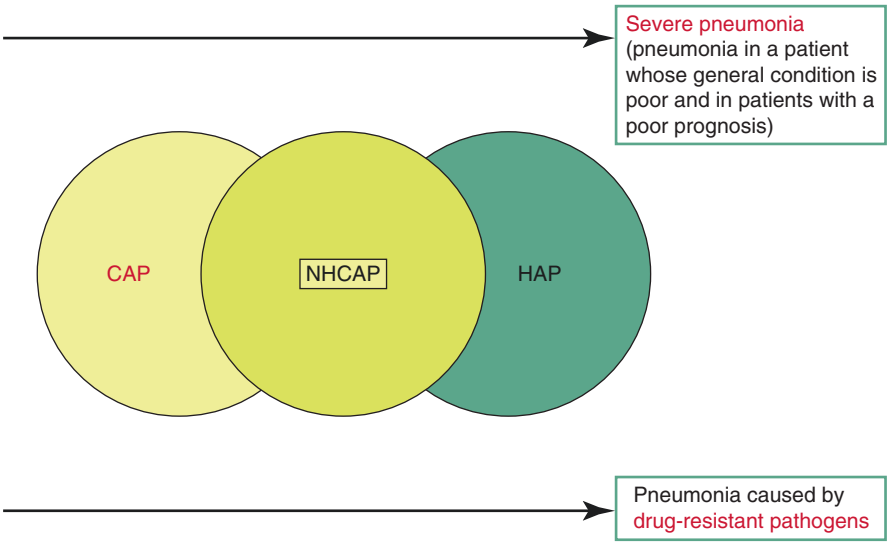

Fig. 21.1 Positioning of CAP, NHCAP, and HAP in Japan. No clear distinctions between CAP, NHCAP, and HAP can be made in Japan. Would cases that have been counted as cases of CAP in Japan (e.g., cases in which the patient is convalescing at home but has frequently been admitted to core hospitals) be counted as cases of HCAP in the United States? Would cases counted as cases of HAP in Japan (e.g., cases of repeated aspiration pneumonia at long-term care hospitals and not at acute care hospitals) be counted as cases of HCAP in the United States?

HCAP patients are more likely to be diagnosed with CAP than with HAP. It is more appropriate to define HCAP as pneumonia that overlaps CAP and HAP and cannot be classified as either CAP or HAP [4, 5]. Furthermore, treatment for HCAP may be similar to the treatment for CAP or to the treatment for HAP, and it differs from hospital to hospital.

There have been reports of data obtained from analyses of HCAP in Japan as well [6, 7]. Since these reports show that drug-resistant pathogens are a more common cause of HCAP than of CAP and also in view of prognoses and other assessments, the treatment of HCAP in Japan should be based on the treatment of HAP. On the other hand, there is a report that most HCAP in Japan is similar to CAP, pneumonia with a poor outcome found largely in elderly patients, rather than HAP, which is drug-resistant pneumonia caused by gram-negative bacteria [8], and it is difficult to evaluate HCAP in Japan in a standardized manner (Fig. 21.1).

Reports in the United States and Europe have also pointed out that HCAP occurs in heterogeneous populations [5, 9, 10], and in view of its original definition, the true nature of HCAP can be described as a mixture of cases of pneumonia with a poor outcome in elderly patients that for the most part consists of "aspiration pneumonia" and drug-resistant pneumonia resulting from an advanced medical care environment.

Furthermore, it has been pointed out that the differences in the healthcare environment between communities or countries are reflected in the incidence of HCAP

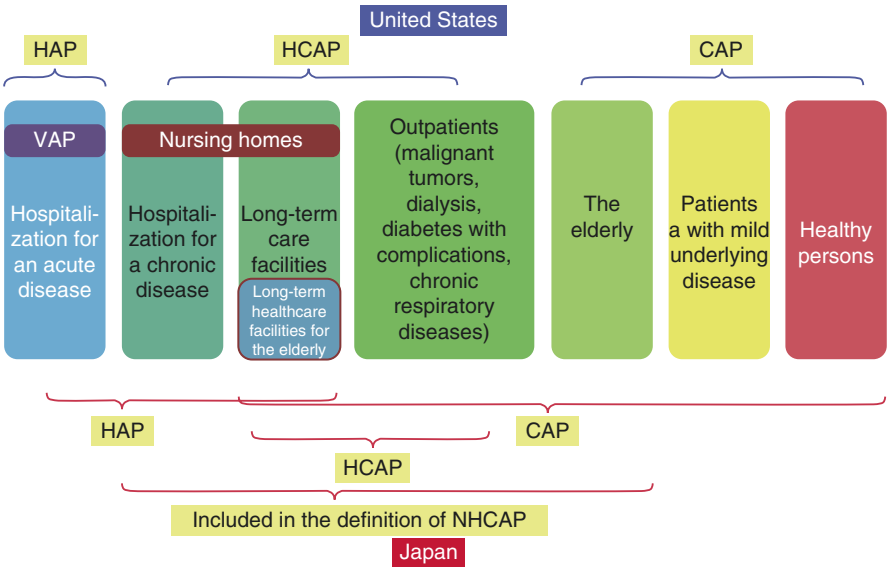

Fig. 21.2 Categories of HAP, HCAP, and CAP by type of facility and type of patient in Japan: realities in the "nursing care insurance system"

and ratio of HCAP cases to HAP or CAP cases, and thus the data have sometimes varied significantly from report to report [4, 6, 11].

In particular, the definition of "hospital" in Japan is very different from its definition in the United States. This is largely because there are many more extended-care facilities, including "nursing homes" and "geriatric hospitals," in the United States, and many cases of pneumonia that have been diagnosed as HCAP in the United States would have been diagnosed as HAP in Japan (Fig. 21.2) [3, 12].

On the other hand, when NHCAP is viewed from a CAP perspective, if a bedridden patient residing at home developed aspiration pneumonia or a dialysis patient with risk factors for involvement by drug-resistant pathogens developed pneumonia and were transported to a nearby core hospital, the patient would be treated for CAP in Japan [2], whereas both would have been treated for HCAP in the United States.

Because Japan has a unique nursing care insurance system and healthcare and nursing care system, caution is required when US definitions are directly applied to the situation in Japan.

From this standpoint, the definitions of NHCAP are suggested by the committee for preparation of clinical practice guidelines for nursing- and *healthcare-associated pneumonia* (*NHCAP*) of the Japanese Respiratory Society (Table 21.1) [1]. The definitions of NHCAP reflect the fact that there are many cases of aspiration pneumonia in the elderly in Japan on the background of the nursing care insurance system, and the committee considers it appropriate to add the term "nursing care" and use the term "nursing- and healthcare-associated pneumonia (NHCAP)" to express

Table 21.1 Definition of NHCAP

1.	Pneumonia diagnosed in a resident of an extended care facility or nursing home
2.	Pneumonia diagnosed in a person who has been discharged from a hospital within the preceding 90 days
3.	Pneumonia diagnosed in an elderly or disabled person who is receiving nursing care
4.	Pneumonia diagnosed in a person who is receiving regular endovascular treatment as an outpatient (dialysis, antibiotic therapy, chemotherapy, immunosuppressant therapy)

Standards for nursing care
Patients whose performance status is PS 3 (capable of only limited self-care, confined to bed or a chair more than 50% of their waking hours) or more
Item 1 includes patients on psychiatric wards

Table 21.2 Main pathogenic mechanism of NHCAP

1.	Aspiration pneumonia
2.	Bacterial pneumonia secondary to influenza
3.	Drug-resistant pneumonia (such as MRSA pneumonia) secondary to endovascular treatment, such as dialysis
4.	Pneumonia caused by opportunistic microorganism during treatment with an immunosuppressive agent or anticancer drug

HCAP in Japan. Naturally, the definition of NHCAP includes drug-resistant pneumonia that occurs during advanced medical care, dialysis and immunosuppressant therapy, and pneumonia caused by opportunistic pathogens. Furthermore, these *guidelines* emphasize that the selection of treatment for NHCAP largely depends on the judgment of the attending physician and should not be selected in a routine manner [1]. NHCAP can be viewed as "HCAP in Japan" or as "the *Nippon* version of HCAP," and it is a highly original concept that reflects the unique conditions within Japan. It is important to take special note of aspiration pneumonia in regard to clinical practice related to NHCAP, because many of the cases of NHCAP are cases of pneumonia in the elderly, including "aspiration pneumonia" and influenza-related pneumonia (Table 21.2) [1, 13, 14].

3 The Concept of Patient Treatment Category

Instead of classifying patients into categories based on the severity of their illness, these *guidelines* suggest classifying patients into "patient treatment categories," which take severity into account [1].

Since the pathology, underlying diseases, and complications of NHCAP patients vary from case to case, it is impossible to make a prognosis based on the severity of the NHCAP, and thus classifying patients with NHCAP according to the severity of their illness is inappropriate.

An NHCAP patient's treatment category should be determined based on an assessment of all of the following: whether drug-resistant pathogens are present,

underlying diseases, complications, nutritional status, psychological and physical activity, and the state of support from other persons responsible for the patient's care [1, 6–8].

The risk factors for involvement by drug-resistant pathogens are a history of antibiotic therapy within the preceding 90 days or current tube feeding. Before determining the patient's treatment category, the attending physician should thoroughly discuss the objectives of treatment with the patient and the patient's family [1, 6].

4 Antibiotics Selection

Treatment strategies should be decided from the standpoint of "respect for autonomy (of the patient)" by the attending physician, who has the best understanding of the history of the patient and the patient's family and their lives and who will respect the wishes of the patient and the patient's family [1].

Although the pathology of CAP and pure HAP is similar, it is particularly evident in Japan that NHCAP occurs in the form of various pathologies in patients from a variety of residential environments who have different underlying diseases and complications, and it is difficult to stratify the cases according to severity or distinguish between different grades of severity. These *guidelines* propose giving priority to the treatment required by the individual patient instead of severity when classifying them, as described below (Fig. 21.3) [1]. Involvement by "high-risk"

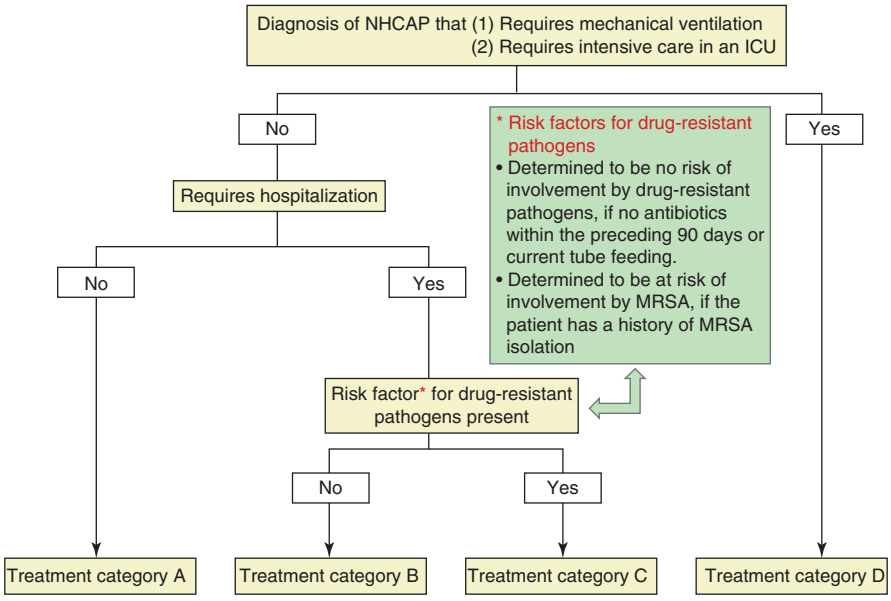

Fig. 21.3 Treatment category algorithm

drug-resistant pathogens, such as *P. aeruginosa*, extended-spectrum β-lactamase (ESBL)-producing enteric bacteria, and MRSA, has been adopted as a criterion for classifying patients according to treatment [1, 3, 4].

According to Fig. 21.3, because there is no risk of involvement by drug-resistant pathogens in patients in treatment category A or treatment category B, a narrow-spectrum antibiotic should be selected in the same manner as for the treatment of CAP, including "aspiration pneumonia." Because they are at risk for involvement by drug-resistant pathogens, patients in treatment category C should be treated with one of the broad-spectrum antibiotics for which a low incidence of adverse reactions has been reported. A powerful broad-spectrum antibiotic, including an antibiotic for the treatment of drug-resistant pathogens and rare pathogens such as *Legionella*, should be selected for the treatment of patients in treatment category D, because of their poor prognosis [1].

5 Vaccines, Infection Control Antimicrobial Stewardship, and Diagnostic Stewardship

In addition to antibiotic therapy, preventive measures such as vaccination are particularly important [1, 4].

Vaccination of nursing home residents with PPSV and PCV is useful in preventing pneumococcal pneumonia and in decreasing the mortality rate [15, 16]. Vaccination of residents of nursing care facilities for the elderly with a combination of influenza vaccine and PPSV/PCV decreases their hospitalization rate for pneumonia [17].

In addition, antimicrobial stewardship team (AST) and infection control team (ICT) have recently been linked to infectious disease (ID) physicians and implemented in clinical settings in Japan [18, 19]. The microbiological effects of an AST and ICT, in addition to diagnostic stewardship team (DST) supported by ID physicians in tertiary hospital, were shown in the significant reduction of antibiotic resistance [20, 21]. These strategies were suggested to be very effective to reduce NHCAP in patients, including most of "aspiration pneumonia" cases and their treatment failure cases.

6 Conclusion

HCAP/NHCAP was usually considered as the pneumonia between CAP and HAP, and among them, NHCAP can be defined as "HCAP in Japan" or as "the *Nippon* version of HCAP." It is important to take care of aspiration pneumonia in regard to clinical practice related to NHCAP, because a lot of NHCAP are cases of pneumonia in the elderly, including "aspiration pneumonia."

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Conflict of Interest None.

References

1. Kohno S, Imamura Y, Shindo Y, et al. Clinical practice guidelines for nursing- and healthcare-associated pneumonia (NHCAP). Respir Investig. 2013;53:103–26.
2. The committee for the Japanese Respiratory Society guidelines in the management of respiratory infections. The Japanese respiratory society guidelines for the management of community-acquired pneumonia in adults. Respirology. 2006;11:S1–S133.
3. The committee for the Japanese Respiratory Society guidelines for the management of respiratory infections. The Japanese Respiratory society guidelines for the management of hospital-acquired pneumonia in adults 2008. Respirology. 2009;14:S1–71.
4. American Thoracic Society and Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med. 2005;171:388–416.
5. Kollef MH, Morrow LE, Baughman RP, et al. Health care-associated pneumonia (HCAP): a critical appraisal to improve identification, management, and outcomes—proceedings of the HCAP summit. Clin Infect Dis. 2008;46:S296–334.
6. Shindo Y, Sato S, Maruyama E, et al. Health-care-associated pneumonia among hospitalized patients in a Japanese community hospital. Chest. 2009;135:633–40.
7. Seki M, Hashiguchi K, Tanaka A, et al. Characteristics and disease severity of healthcare-associated pneumonia among patients in a hospital in Kitakyushu Jpn. J Infect Chemother. 2011;17:363–9.
8. Maruyama T, Niederman MS, Kobayashi T, et al. A prospective comparison of nursing home-acquired pneumonia with hospital-acquired pneumonia in non-intubated elderly. Respir Med. 2008;102:1287–95.
9. Brito V, Niederman MS. Healthcare-associated pneumonia is a heterogeneous disease, and all patients do not need the same broad-spectrum antibiotic therapy as complex nosocomial pneumonia. Curr Opin Infect Dis. 2009;22:316–25.
10. Ewig S, Welte T, Chastre J, et al. Rethinking the concepts of community-acquired and health-care-associated pneumonia. Lancet Infect Dis. 2010;10:279–87.
11. Carratalà J, Mykietiuk A, Fernández-Sabé N, et al. Health care-associated pneumonia requiring hospital admission: epidemiology, antibiotic therapy, and clinical outcomes. Arch Intern Med. 2007;167:1393–9.
12. Seki M, Watanabe A, Mikasa K, Kadota J, Kohno S. Revision of the severity rating and classification of hospital-acquired pneumonia in the Japanese respiratory society guidelines. Respirology. 2008;13:880–8.
13. Teramoto S, Kawashima M, Komiya K, et al. Health-care-associated pneumonia may be primary due to aspiration pneumonia. Chest. 2009;136:1702–3.
14. Seki M, Yanagihara K, Higashiyama Y, Fukuda Y, Kaneko Y, Ohno H, Miyazaki Y, Hirakata Y, Tomono K, Kadota J, Tashiro T, Kohno S. Immunokinetics in severe pneumonia due to influenza virus and bacteria coinfection in mice. Eur Respir J. 2004;24:143–9.
15. Maruyama T, Taguchi O, Niederman MS, et al. Efficacy of 23-valent pneumococcal vaccine in preventing pneumonia and improving survival in nursing home residents: double blind, randomized and placebo controlled trial. Br Med J. 2010;340:c1104.
16. Huijts SM, Coenjaerts FEJ, Bolkenbaas M, van Werkhoven CH, Grobbee DE, Bonten MJM. CAPiTA study team. The impact of 13-valent pneumococcal conjugate vaccination

on virus-associated community-acquired pneumonia in elderly: exploratory analysis of the CAPiTA trial. Clin Microbiol Infect. 2018;24(7):764–70.
17. Kawakami K, Ohkusa Y, Kuroki R, et al. Effectiveness of pneumococcal polysaccharide vaccine against pneumonia and cost analysis for the elderly who receive seasonal influenza vaccine in Japan. Vaccine. 2010;28:7063–9.
18. Maeda M, Muraki Y, Kosaka T, Yamada T, Aoki Y, Kaku M, Kawaguchi T, Seki M, Tanabe Y, Fujita N, Morita K, Yanagihara K, Yoshida K, Niki Y. The first nationwide survey of antimicrobial stewardship programs conducted by the Japanese Society of Chemotherapy. J Infect Chemother. 2019;25:83–8. https://doi.org/10.1016/j.jiac.2018.11.001.
19. Miyawaki K, Miwa M, Seki M, Asari S, Tomono K, Kurokawa N. Correlation between the consumption of meropenem or doripenem and meropenem susceptibility of *Pseudomonas aeruginosa* in a university hospital in Japan. Biol Pharm Bull. 2012;35:946–9.
20. Seki M, Watanabe Y. The microbiological effects of antimicrobial stewardship program and infection control in Japan. J Prev Infect Cntrol. 2017;3(2):9. https://doi.org/10.21767/2471-9668.100034.
21. Watanabe Y, Seki M. Improvement of antibiotics susceptibility of *Escherichia coli* in a tertiary hospital in Japan. Microbiol Res J Int. 2019;28(1):1–5.

Chapter 22
Sleep Apnea, Hypnotics, and Aspiration Pneumonia: Is There Any Association Between Sleep Apnea and Aspiration Pneumonia?

Yasuhiro Yamaguchi

Abstract The association between swallowing dysfunction and sleep apnea has been confirmed from multiple facets. Patients with obstructive sleep apnea (OSA) showed a significant delay in the onset of the swallowing reflex compared to the healthy controls. Pathological evaluations revealed neuronal injuries of the pharynx in patients with OSA. Furthermore, the coordination between respiration and swallowing was impaired in patients with OSA. OSA also worsened the gastroesophageal reflux disease, which can be a risk factor for aspiration. Finally, patients with OSA were frequently complicated with other comorbidities including cerebrovascular diseases. Possibly owing to these deficits, some investigations had revealed a significant association between sleep apnea and the development of pneumonia. Dysphagia induced by OSA was reversible with the continuous positive airway pressure (CPAP) therapy. In addition, OSA was a major risk factor for the poor prognosis and frequent exacerbations of chronic obstructive pulmonary diseases, and the CPAP therapy proved effective in preventing these harmful effects. Administration of benzodiazepines or benzodiazepine-related drugs was also significantly associated with the development of pneumonia.

Keywords Sleep apnea · Gastroesophageal reflux · Continuous positive airway pressure · Chronic obstructive pulmonary disease · Benzodiazepines

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1 Introduction

1.1 Swallowing and Breathing

Leopold and Kagel described five stages of ingestion: preoral, preparatory, lingual, pharyngeal, and esophageal [1]. Any disturbance in this ingestion process can contribute to aspiration and consequently to aspiration pneumonia. Swallowing corresponds to the lingual, pharyngeal, and esophageal stages, in which more than 25 muscles and multiple cranial nerves function together. These muscles and nerves also perform other physiological functions in the upper airways, such as airway dilation during breathing. Considering these physiological linkages, estimating an association between aspiration and breathing disorders is reasonable.

1.2 Breathing Disorders During Sleep

Obstructive sleep apnea (OSA)-hypopnea is a major breathing disorder during sleep. It is defined as breathing cessation for over 10 seconds during sleep due to upper airway obstruction. Hypopnea is defined as reduced breathing for over 10 seconds during sleep with or without oxygen desaturation or arousal. The diagnostic criterion of OSA is the number of apnea and hypopnea events (apnea-hypopnea index, AHI) >5.0/h with some symptoms. Patients with severe OSA have an AHI score >30.0 events/h. However, the precise diagnostic criteria are inconsistent and complicated. Some studies referenced in this chapter did not evaluate the symptoms or even use other cutoff points of AHI.

Patients with OSA show sleep fragmentation and a short slow-wave sleep. The poor sleep quality frequently causes excessive daytime sleepiness and occasionally causes traffic accidents resulting from unintentional napping. Furthermore, OSA is strongly associated with hyperactivity of the sympathetic nervous system during sleep. In addition, the inspiratory effort against the obstructed airways causes an extremely low intrathoracic pressure, leading to an increase in the venous return. These effects result in frequent incidence of hypertension, cardiovascular events, and stroke in patients with OSA [2].

1.3 Continuous Positive Airway Pressure Therapy

The continuous positive airway pressure (CPAP) therapy is the gold standard treatment for OSA. With the CPAP therapy, the number of events of obstructive apnea and hypopnea decreases dramatically. More importantly, the CPAP therapy decreases the sympathetic nervous system activity during sleep, thus lowering the

blood pressure. The CPAP therapy prevents lowering the intrathoracic pressure by opening the upper airways and decreases the volume of the venous return. It can decrease the nocturnal urinary volume and frequency. Furthermore, the previous observational study revealed that significantly fewer cardiovascular events occurred in patients with OSA who adhered to the CPAP therapy compared to those who had not accepted the CPAP therapy [3].

2 Sleep Apnea and Swallowing Dysfunction

2.1 Impaired Swallowing Function in Patients with Sleep Apnea

Teramoto et al. evaluated the swallowing reflex using the swallowing provocation test in patients with OSA after excluding those with cerebrovascular diseases, alcoholism, or neuromuscular diseases [4]. The swallowing provocation test records the pharyngeal constriction and breathing after dripping 0.4–2.0 mL of water into the pharynx via a thin nasal tube. It can measure the precise latent time in the onset of the swallowing reflex and the inspiratory suppression time (Fig. 22.1a). Patients with OSA showed a significantly longer latent time in the onset of the swallowing reflex and a shorter inspiratory suppression time (Fig. 22.1b, c). Because the standard latent time before the onset of the swallowing reflex is less than 3.0 second, some patients with OSA showed a significant delay, while the results of the control patients were within normal limits.

These findings have been confirmed using other methods. For example, Nguyen et al. measured the endoscopic sensory testing (EST) threshold of the upper airways [5]. This technique involves the delivery of 50-millisecond air pulses, ranging from 2 to 10 mmHg in intensity, and evaluates the patients' ability to detect the air pulse. Many patients with OSA showed a high EST threshold of the oropharynx and velopharynx, while most control patients showed a low EST threshold. The EST thresholds of the lips did not differ between patients with OSA and control patients. It suggests that the sensory disturbances occurred only at the site where the airway occluded during sleep apnea.

In a recent systematic review, all the 11 included studies had revealed abnormalities in the swallowing function in patients with OSA [6]. Teramoto et al. [7] reported a correlation between the nocturnal nadir percutaneous oxygen saturation (SpO_2) and the latent time in the onset of the swallowing reflex. However, some studies showed no correlation between AHI and the severity of swallowing dysfunction. These inconsistencies could be partially attributed to the differences in the techniques and parameters used to measure the swallowing function.

The study by Jäghagen et al. [8] reported that even snorers showed more pharyngeal swallowing dysfunction compared to the healthy controls, suggesting that early stages of upper airway resistance impair the swallowing function.

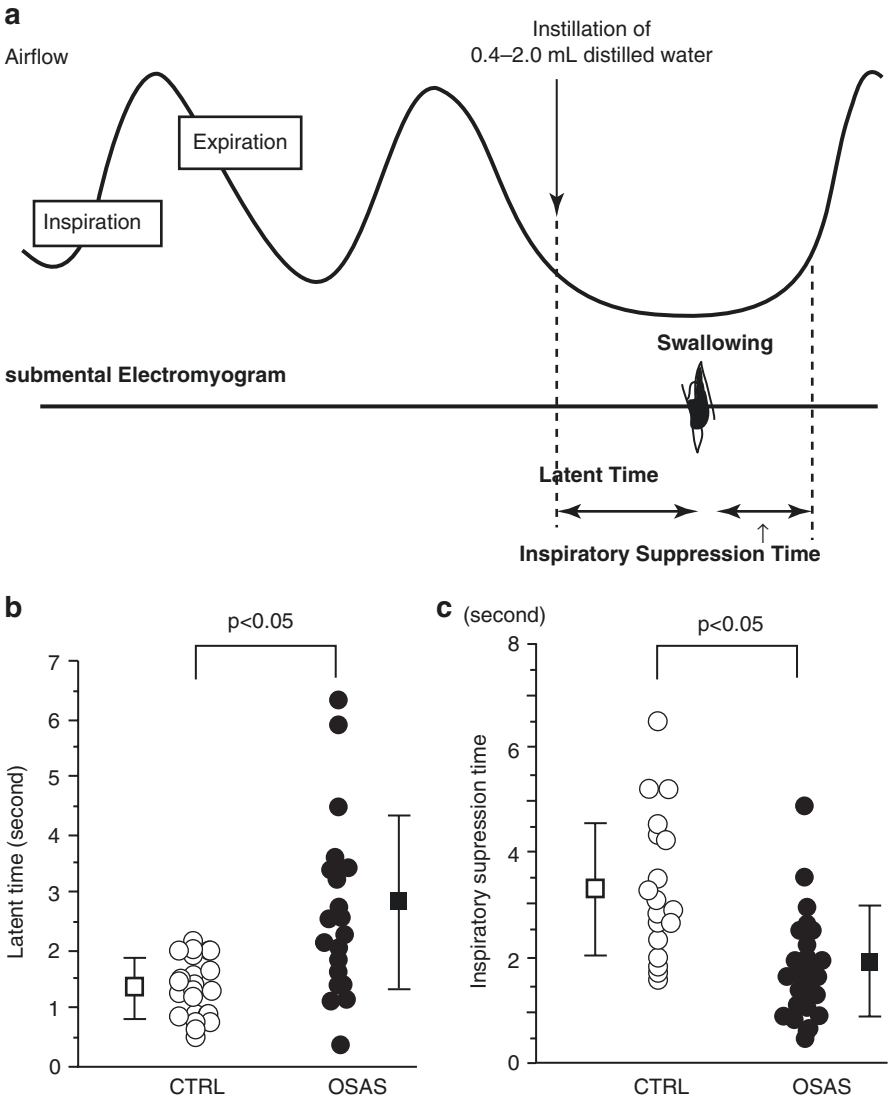

Fig. 22.1 Swallowing reflex in patients with obstructive sleep apnea. (**a**) The figure illustrates the latent time and inspiratory suppression time in the swallowing provocation test. (**b**) The latent time was significantly longer in patients with obstructive sleep apnea syndrome (OSAS) patients than in the control (CTRL) patients [4]. (**c**) The inspiratory suppression time was significantly shorter in patients with OSAS than in the CTRL patients [4]

2.2 Mechanism of Swallowing Dysfunction Caused by OSA

Previous evaluations of the pharyngeal muscles in patients with snoring or OSA revealed progressive local neurogenic changes in the myofibers. These findings were strongly supported by the observation of surgical samples from the soft palate, which showed more prominent axon degeneration in patients with snoring or sleep apnea compared to the healthy controls [9]. These neural injuries worsen both the swallowing dysfunction and breathing disorder.

It is difficult to elucidate the mechanism underlying the development of nerve degeneration in the pharynx caused by snoring and sleep apnea. Shah et al. speculated that the most likely cause is traumatic snoring vibrations and tissue stretch [9]. This hypothesis is consistent with the finding that even snorers show swallowing dysfunction. However, another study suggested that the nocturnal decrease in SpO_2 and hypercapnia worsen the swallowing function [7].

Finally, many patients with OSA have multiple comorbidities, which can be associated with the swallowing dysfunction, especially in the elderly patients.

2.3 CPAP Therapy and the Swallowing Function

Whether the CPAP therapy can improve the swallowing function in patients with OSA or not has not been well-evaluated. In a case series by Okada et al., parameters of the swallowing function improved after the CPAP therapy [10]. Similarly, Kimoff et al. reported that patients with OSA showed significantly improved vibration sensations after the CPAP therapy, while the patients who did not undergo the CPAP therapy showed no changes [11]. In a recent study, 9 of the 11 patients with OSA who had shown swallowing dysfunction exhibited improvement in dysphagia after undergoing the CPAP therapy for 3 months [12]. They also showed improvement in scores of Swallowing Quality of Life, which is a dysphagia-specific quality-of-life questionnaire. These findings indicated that the CPAP therapy can treat impaired swallowing functions in the short term. They also suggest that OSA almost directly causes a reversible deterioration in the swallowing function.

Meanwhile, many patients with OSA have multiple comorbidities, which can be associated with swallowing dysfunction, especially in the elderly patients. In these cases, the swallowing dysfunction would not be easily or completely improve with the CPAP therapy. Most patients with OSA were young adults in the investigations that showed reversal in the swallowing dysfunction with the CPAP therapy [10–12]. While pneumonia occurs predominantly in the elderly patients, the efficacy of the CPAP therapy in improving the swallowing function cannot be generalized to all patients with dysphagia.

2.4 Impaired Coordination Between Respiration and Swallowing in Patients with OSA

The coordination between respiration and swallowing is important to prevent aspiration. Breathing must be ceased during swallowing. When a pharyngeal constriction incompletely propels the food bolus in the esophagus, subsequent breathing must be regulated to avoid inhaling food. Therefore, sufficient inspiratory suppression time is important (Fig. 22.1a). Furthermore, expiration follows breathing cessation in most swallowing events for healthy adults. Previous investigations indicated that patients with Parkinson's disease or chronic obstructive pulmonary disease (COPD) showed an impaired coordination between respiration and swallowing, i.e., frequent swallowing during inhalation [13, 14].

Sato et al. evaluated deglutition during sleep using electromyography of the thyrohyoid and suprahyoid muscles in addition to the conventional polysomnography [15]. They found that most deglutition occurred in association with arousal following apnea or hypopnea. Because of the thirst for air when restarting respiration, a strong breathing effort and decreased intrathoracic pressure heighten the risk of aspiration. Furthermore, swallowing frequently occurred during inspiration in patients with severe OSA. However, the CPAP therapy markedly reduced the frequency of swallowing during inspiration [16].

2.5 Sleep Apnea and Gastroesophageal Reflux

With an airway obstruction, an intense breathing effort prominently lowers the intrathoracic pressure. The low intrathoracic pressure can induce a gastroesophageal reflux. Because gastroesophageal refluxes are common in obese patients, the data on the association between gastroesophageal refluxes and OSA have been inconsistent. However, a recent meta-analysis confirmed a significant association between obstructive sleep apnea syndrome and gastroesophageal reflux disease, with a pooled odds ratio (OR) of 1.75 (95% confidence interval (CI) 1.18–2.59, $P < 0.05$) [17]. The gastroesophageal reflux disease is a common risk factor for aspiration.

3 Association Between OSA and Respiratory Diseases

3.1 Pneumonia in Patients with OSA

Considering the associations between OSA and swallowing impairment, it is reasonably estimated that pneumonia occurs more frequently among patients with OSA. We had evaluated the association between AHI and respiratory infections in tube-fed patients with cerebrovascular diseases [18]. In this study, patients with a recent history of respiratory infections showed significantly higher AHI scores than patients without a history of respiratory infections (Fig. 22.2a, b). Likewise, the

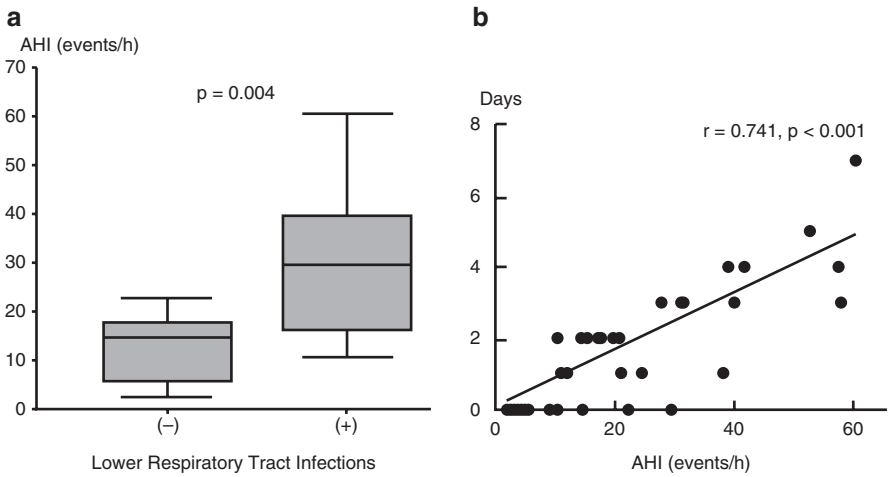

Fig. 22.2 Correlation between the duration of fever and the apnea-hypopnea index [18]. (**a**) Patients with respiratory infections showed significantly higher apnea-hypopnea index (AHI) scores. (**b**) The AHI scores significantly correlated with the duration of febrile days with body temperature ≥38.0 °C because of probable respiratory infections in the previous 90 days among the bedridden elderly adults without oral intake

days with fever >38.0 °C with no other specific causes significantly correlated with high AHI scores, suggesting frequent micro-aspirations in patients with higher AHI scores. Morimoto et al. reported an association between mixed sleep apnea and mortality from pneumonia in the elderly inpatients [19].

Other recent investigations have revealed an association between OSA and pneumonia in younger patients. A nationwide population-based study in Taiwan showed that pneumonia occurred 1.2 times more frequently in patients with OSA compared to the matched controls [20]. Chiner et al. used a respiratory polygraph in patients admitted for pneumonia and the matched controls admitted for other infectious diseases [21] and found that 25.6% of the patients with community-acquired pneumonia showed an AHI score >30 events/h.

It is difficult to determine if sleep apnea contributes to the development of pneumonia or some common factors contribute to the breathing disorder and development of pneumonia. Likewise, whether the CPAP therapy can prevent pneumonia or not remains to be evaluated.

3.2 Combination of Chronic Respiratory Diseases and OSA

Patients with COPD show various manifestations in breathing and SpO_2 during sleep. Some patients with COPD also have OSA, which is known as the overlap syndrome. Because both COPD and OSA are common diseases in adults, it remains to be clarified if OSA occurs more frequently in patients with COPD than in the general population or the overlap is merely incidental. It is clinically important to know that the prognosis

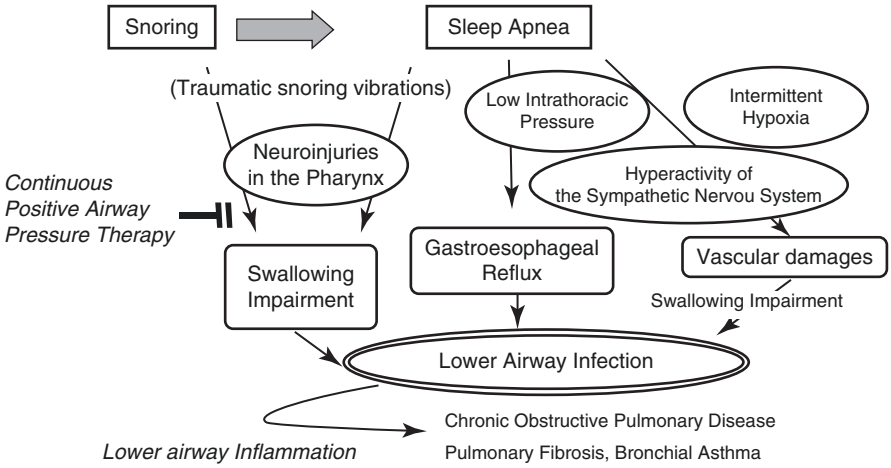

Fig. 22.3 Effects of snoring and the obstructive sleep apnea on lower respiratory diseases. Many previous investigations had revealed an association between swallowing dysfunction and sleep apnea. Histological evaluations had shown neuronal injuries of the pharynx in patients with obstructive sleep apnea (OSA), perhaps because of traumatic snoring vibrations and tissue stretch. OSA also worsens the gastroesophageal reflux disease and may be associated with cerebrovascular diseases. Possibly owing to these deficits, a significant association between OSA and pneumonia incidence was seen. In addition, the complications of OSA are major risk factor for the poor prognosis and frequent exacerbations of chronic obstructive pulmonary diseases. Dysphagia induced by snoring or OSA was reversible with the continuous positive airway pressure therapy

of patients with overlapping COPD and OSA is poorer than that of patients with COPD alone [22]. Moreover, patients with an overlap who used the CPAP therapy showed less frequent exacerbation and lower mortality than the patients who did not use the CPAP therapy [22]. Likewise, some recent investigations suggested the importance of OSA in patients with bronchial asthma and pulmonary fibrosis [23, 24].

The mechanism underlying the increased risk of exacerbation of COPD in patients with OSA remains unknown. OSA may be associated with more intense pulmonary hypertension and more often causes cardiovascular diseases, which can also be a risk factor for frequent exacerbations. However, infections more commonly trigger the exacerbations of COPD. OSA can also contribute to swallowing dysfunction and augment gastroesophageal reflux, resulting in frequent airway infections [25]. OSA modulates the course of chronic respiratory diseases through various mechanisms (Fig. 22.3).

4 Hypnotics and Pneumonia

4.1 Association Between the Use of Hypnotics and the Development of Pneumonia

While the prescription of hypnotics is increasing in Japan, many adverse events have been shown. Maeda et al. quantified the adverse effects of the regular use of triazolam in a retrospective study [26]. They showed that the risk for pneumonia increased by approximately 40% in the elderly patients who had been prescribed with triazolam for 180 days or more in a year. A systematic review and meta-analysis also confirmed that the use of benzodiazepines or benzodiazepine-related drugs is a significant risk factor for pneumonia [27]. They found an increased risk of pneumonia among current (OR = 1.4; 95% CI, 1.22–1.6) and recent (OR = 1.38; 95% CI, 1.06–1.8) users of benzodiazepines or benzodiazepine-related drugs, but not among the past users (OR = 1.11; 95% CI, 0.96–1.27).

Furthermore, hypnotics were strongly associated with pneumonia incidence in the patients who frequently had swallowing dysfunction. A population-based retrospective cohort study in Taiwan revealed 2.21 times higher incidence of chronic-onset poststroke pneumonia [28]. Likewise, Taipare et al. reported an increased risk of pneumonia in benzodiazepine users among community-dwelling patients with Alzheimer's disease [29]. These studies strongly suggested that benzodiazepine use heightens the risk of aspiration pneumonia.

Few investigations directly evaluated the association between benzodiazepine use and swallowing dysfunction. The mechanism underlying the effect of hypnotics on the risk of pneumonia remains unknown. Joya et al. evaluated the occurrence of infection in the US Food and Drug Administration files systematically [30]. As all the included studies were randomized clinical trials, the bias may be little. Both eszopiclone and zolpidem increased the risk of infection. Due to variations in the terms of infection and the short drug-exposure period, it is difficult to statistically show which infection would increase with the use of eszopiclone or zolpidem. However, the significant increase in the total number of infections suggested that hypnotics may be associated with the whole immune function. Another hypothesis states that eszopiclone or zolpidem can worsen gastroesophageal reflux because benzodiazepine agonists might relax the lower esophageal sphincter [30]. Gastroesophageal reflux is associated with various types of upper and lower airway inflammations, including pneumonia.

5 Conclusion

While many investigations on OSA have been focused on vascular diseases, the association between swallowing function and OSA is relevant for preventing pneumonia and controlling various chronic respiratory diseases, which can be exacerbated through airway inflammation. OSA can be a key factor connecting the upper and lower airway diseases.

References

1. Teramoto S, Sudo E, Matsuse T, Ohga E, Ishii T, Ouchi Y, Fukuchi Y. Impaired swallowing reflex in patients with obstructive sleep apnea syndrome. Chest. 1999;116:17–21.
2. Leopold NA, Kagel MC. Dysphagia--ingestion or deglutition?: a proposed paradigm. Dysphagia. 1997;12:202–6.
3. Budhiraja R, Budhiraja P, Quan SF. Sleep-disordered breathing and cardiovascular disorders. Respir Care. 2010;55:1322–32. Discussion 1330–2
4. Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet. 2005;365:1046–53.
5. Nguyen AT, Jobin V, Payne R, Beauregard J, Naor N, Kimoff RJ. Laryngeal and velopharyngeal sensory impairment in obstructive sleep apnea. Sleep. 2005;28:585–93.
6. Ghannouchi I, Speyer R, Doma K, Cordier R, Verin E. Swallowing function and chronic respiratory diseases: systematic review. Respir Med. 2016;117:54–64. https://doi.org/10.1016/j.rmed.2016.05.024.
7. Teramoto S, Ishii T, Matsuse T. Relationship between swallowing function and gas exchange during day and night in patients with obstructive sleep apnea syndrome. Dysphagia. 2001;16:249–53.
8. Jäghagen EL, Berggren D, Isberg A. Swallowing dysfunction related to snoring: a videoradiographic study. Acta Otolaryngol. 2000;120:438–43.
9. Shah F, Holmlund T, Levring Jäghagen E, Berggren D, Franklin K, Forsgren S, Stål P. Axon and Schwann cell degeneration in nerves of upper airway relates to pharyngeal dysfunction in snorers and patients with sleep apnea. Chest. 2018;154:1091–8. https://doi.org/10.1016/j.chest.2018.06.017.
10. Okada S, Ouchi Y, Teramoto S. Nasal continuous positive airway pressure and weight loss improve swallowing reflex in patients with obstructive sleep apnea syndrome. Respiration. 2000;67:464–6.
11. Kimoff RJ, Sforza E, Champagne V, Ofiara L, Gendron D. Upper airway sensation in snoring and obstructive sleep apnea. Am J Respir Crit Care Med. 2001;164:250–5.
12. Caparroz FA, de Almeida Torres Campanholo M, Sguillar DA, Haddad L, Park SW, Bittencourt L, Tufik S, FLM H. A pilot study on the efficacy of continuous positive airway pressure on the manifestations of dysphagia in patients with obstructive sleep apnea. Dysphagia. 2019;34:333–40. https://doi.org/10.1007/s00455-018-9944-1.
13. Gross RD, Atwood CW Jr, Ross SB, Olszewski JW, Eichhorn KA. The coordination of breathing and swallowing in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2009;179:559–65. https://doi.org/10.1164/rccm.200807-1139OC.
14. Troche MS, Huebner I, Rosenbek JC, Okun MS, Sapienza CM. Respiratory-swallowing coordination and swallowing safety in patients with Parkinson's disease. Dysphagia. 2011;26:218–24. https://doi.org/10.1007/s00455-010-9289-x.

15. Sato K, Nakashima T. Sleep-related deglutition in patients with sleep apnea-hypopnea syndrome. Ann Otol Rhinol Laryngol. 2009;118:30–6.
16. Sato K, Umeno H, Chitose S, Nakashima T. Sleep-related deglutition in patients with OSAHS under CPAP therapy. Acta Otolaryngol. 2011;131:181–9. https://doi.org/10.3109/00016489.2010.520166.
17. Wu ZH, Yang XP, Niu X, Xiao XY, Chen X. The relationship between obstructive sleep apnea hypopnea syndrome and gastroesophageal reflux disease: a meta-analysis. Sleep Breath. 2019;23:389–97. https://doi.org/10.1007/s11325-018-1691-x.
18. Ishii M, Yamaguchi Y, Yamamoto H, Ouchi Y, Osumi S, Nakamura T. Relationship between sleep apnea and respiratory infections in bedridden elderly individuals on tube feeding. J Am Geriatr Soc. 2012;60:790–2. https://doi.org/10.1111/j.1532-5415.2011.03874.x.
19. Morimoto S, Takahashi T, Okaishi K, Okuro M, Nakahashi T, Sakamoto D, et al. Sleep apnoea syndrome as a risk for mortality in elderly inpatients. J Int Med Res. 2012;40:601–11.
20. Su VY, Liu CJ, Wang HK, Wu LA, Chang SC, Perng DW, et al. Sleep apnea and risk of pneumonia: a nationwide population-based study. CMAJ. 2014;186:415–21. https://doi.org/10.1503/cmaj.131547.
21. Chiner E, Llombart M, Valls J, Pastor E, Sancho-Chust JN, Andreu AL, Sánchez-de-la-Torre M, Barbé F. Association between obstructive sleep apnea and community-acquired pneumonia. PLoS One. 2016;11:e0152749. https://doi.org/10.1371/journal.pone.0152749.
22. Marin JM, Soriano JB, Carrizo SJ, Boldova A, Celli BR. Outcomes in patients with chronic obstructive pulmonary disease and obstructive sleep apnea: the overlap syndrome. Am J Respir Crit Care Med. 2010;182:325–31. https://doi.org/10.1164/rccm.200912-1869OC.
23. Mermigkis C, Bouloukaki I, Schiza SE. Sleep as a new target for improving outcomes in idiopathic pulmonary fibrosis. Chest. 2017;152:1327–38. https://doi.org/10.1016/j.chest.2017.07.019.
24. Davies SE, Bishopp A, Wharton S, Turner AM, Mansur AH. The association between asthma and obstructive sleep apnea (OSA): a systematic review. J Asthma. 2019 Feb;56(2):118–29. https://doi.org/10.1080/02770903.2018.1444049.
25. Teramoto S. A possible pathological link among swallowing dysfunction, gastro-esophageal reflex, and sleep apnea in acute exacerbation in COPD patients. Int J Chron Obstruct Pulmon Dis. 2016;11:147–50. https://doi.org/10.2147/COPD.S99663.
26. Maeda T, Babazono A, Nishi T, Yasui M. Quantification of adverse effects of regular use of triazolam on clinical outcomes for older people with insomnia: a retrospective cohort study. Int J Geriatr Psychiatry. 2016;31:186–94. https://doi.org/10.1002/gps.4310.
27. Sun GQ, Zhang L, Zhang LN, Wu Z, Hu DF. Benzodiazepines or related drugs and risk of pneumonia: a systematic review and meta-analysis. Int J Geriatr Psychiatry. 2019;34:513–21. https://doi.org/10.1002/gps.5048.
28. Lin SM, Yang SH, Liang CC, Huang HK, Loh CH. Association between benzodiazepine use and risks of chronic-onset poststroke pneumonia: a population-based cohort study. BMJ Open. 2019;9:e024180. https://doi.org/10.1136/bmjopen-2018-024180.
29. Taipale H, Tolppanen AM, Koponen M, Tanskanen A, Lavikainen P, Sund R, Tiihonen J, Hartikainen S. Risk of pneumonia associated with incident benzodiazepine use among community-dwelling adults with Alzheimer disease. CMAJ. 2017;189:E519–29. https://doi.org/10.1503/cmaj.160126.
30. Joya FL, Kripke DF, Loving RT, Dawson A, Kline LE. Meta-analyses of hypnotics and infections: eszopiclone, ramelteon, zaleplon, and zolpidem. J Clin Sleep Med. 2009;5:377–83.