

## REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

## Aspiration Pneumonia

Lionel A. Mandell, M.D., and Michael S. Niederman, M.D.

ASPIRATION PNEUMONIA IS BEST CONSIDERED NOT AS A DISTINCT ENTITY but as part of a continuum that also includes community- and hospital-acquired pneumonias. It is estimated that aspiration pneumonia accounts for 5 to 15% of cases of community-acquired pneumonia, but figures for hospital-acquired pneumonia are unavailable.<sup>1</sup> Robust diagnostic criteria for aspiration pneumonia are lacking, and as a result, studies of this disorder include heterogeneous patient populations.

Aspiration of small amounts of oropharyngeal secretions is normal in healthy persons during sleep, yet microaspiration is also the major pathogenetic mechanism of most pneumonias.<sup>2</sup> Large-volume aspiration (macroaspiration) of colonized oropharyngeal or upper gastrointestinal contents is the sine qua non of aspiration pneumonia. Variables affecting patient presentation and disease management include bacterial virulence, the risk of repeated events, and the site of acquisition (nursing home, hospital, or community). According to this spectrum, patients labeled as having aspiration pneumonia usually represent a clinical phenotype with risk factors for macroaspiration and involvement of characteristic anatomical pulmonary locations. Aspiration syndromes may involve the airways or pulmonary parenchyma, resulting in a variety of clinical presentations.<sup>3</sup>

This review focuses on aspiration involving the lung parenchyma, primarily aspiration pneumonia and chemical pneumonitis. Aspiration of noninfectious material such as blood or a foreign body is also important. Aspiration pneumonia is an infection caused by specific microorganisms, whereas chemical pneumonitis is an inflammatory reaction to irritative gastric contents. Our understanding of the interaction between bacteria and the lung has improved. We examine this improvement, along with changing concepts of the microbiology and pathogenesis of aspiration pneumonia. We also examine the clinical features, diagnosis, treatment, and prevention of both aspiration pneumonia and chemical pneumonitis, as well as the risk factors.

---

 CHANGING MICROBIOLOGIC AND PATHOGENETIC CONCEPTS  
OF ASPIRATION PNEUMONIA
 

---

Our understanding of normal lower-airway microbiota in humans has evolved with the use of targeted polymerase-chain-reaction studies, sequencing of bacterial 16S ribosomal RNA genes, and metagenomics. A recent study of oral microbiota in patients with acute stroke identified 103 different bacterial phylotypes, 29 of which had not been reported previously.<sup>4</sup> Whether these new microbes are pathogens is uncertain.

The Human Microbiome Project has helped define the role that intestinal microorganisms play in the development of mucosal immunity and in the interplay between health and disease. Studies of the lung microbiome have challenged our

From McMaster University, Hamilton, ON, Canada (L.A.M.); and Weill Cornell Medical College, New York (M.S.N.). Address reprint requests to Dr. Mandell at lmandell@mcmaster.ca.

N Engl J Med 2019;380:651-63.

DOI: 10.1056/NEJMr1714562

Copyright © 2019 Massachusetts Medical Society.

assumptions of lung sterility and of bacterial access to the lungs through aspiration (microaspiration or macroaspiration) and inhalation. Specifically, genomic methods have defined a complex taxonomic landscape of bacteria in the lung and revealed the presence of diverse communities of microbiota. We are still learning about the role of the microbiome in health and disease, as well as in the pathogenesis of pneumonia.<sup>5,6</sup> In the healthy state, the immune tone of the airways and alveoli appears to be calibrated by the bacteria constituting the lung microbiota, an observation recently reported in both healthy humans and experimental animal models.<sup>7,8</sup> Concepts of virulence have also changed; virulence is defined as “the relative capacity of a microorganism to cause damage to a host.”<sup>9</sup> Infection is not simply the result of bacterial replication or of bacterial gene products; it is also a consequence of the host response, resultant inflammation, and tissue damage.<sup>9,10</sup>

Models proposed to explain the possible role of the lung microbiome in pneumonia include the adapted island model of lung biogeography, effects of environmental gradients on lung microbiota (e.g., regional differences in oxygen tension and nutrient availability in the lungs), and finally, pneumonia as an emerging phenomenon in the complex adaptive system of the lung microbial ecosystem.<sup>11,12</sup> The stability of the lung microbiome is probably maintained by a balance of immigration and elimination of bacteria and by feedback loops. Immigration involves bacterial movement from the oropharynx to the lung primarily by means of microaspiration, and elimination mainly occurs through ciliary clearance and coughing. Negative and positive feedback loops can suppress or magnify signals, respectively, such as those for bacterial growth. An inflammatory event may lead to epithelial and endothelial injury, creating a positive feedback loop that can promote inflammation, disrupt bacterial homeostasis, and increase susceptibility to infection. The complex adaptive system model suggests that acute bacterial pneumonia results from enhancement of a growth-promoting signal by a positive feedback loop. This may result in a rapid shift from a diverse microbial mixture to dominance by a single species (e.g., *Streptococcus pneumoniae* or *Pseudomonas aeruginosa*).<sup>12</sup> Various signaling molecules in humans, including neurotransmitters, cytokines, and hormones

such as glucocorticoids, have been shown in vitro to promote the growth of *S. pneumoniae* and certain gram-negative rods.<sup>13-16</sup>

One hypothesis linking the airway microbiome with aspiration pneumonia is that illness may result in a change in the lung microbiota (dysbiosis), which may, in turn, interfere with or impair pulmonary defenses. A macroaspiration event, particularly in a patient with risk factors for impaired bacterial elimination, such as reduced consciousness or an impaired cough reflex, could then overwhelm the elimination side of the immigration–elimination balance, further disrupting bacterial homeostasis and triggering an increase in a positive feedback loop leading to acute infection.

Bacteria may colonize various sites in the human oral cavity, such as the gingiva, dental plaque, and tongue.<sup>17,18</sup> Pathogenic bacteria, including gram-negative species that are not seen in the normal host, may emerge in the elderly, as well as in patients in nursing homes or hospitals and those with nasogastric tubes.<sup>19-21</sup> Cleavage of cell-surface fibronectin exposes receptors for gram-negative rods on underlying airway epithelial cells and is more closely correlated with host factors such as acute illness than with the site of care.<sup>22</sup>

In the 1970s, anaerobes with or without aerobes were the predominant pathogens in aspiration pneumonia.<sup>23-26</sup> More recently, there has been a shift to bacteria usually associated with community- and hospital-acquired pneumonias, and anaerobes are recovered less frequently.<sup>26</sup> One study of aspiration pneumonia in patients in the intensive care unit showed that in community-acquired cases, the main isolates were *S. pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae*, and Enterobacteriaceae, whereas gram-negative bacilli, including *P. aeruginosa*, were found without anaerobes in hospital-acquired cases.<sup>27</sup> Another study assessed the incidence of anaerobic bacteria in patients with ventilator-associated pneumonia and in those with aspiration pneumonia.<sup>28</sup> Bacterial pneumonia was diagnosed in 63 patients with ventilator-associated pneumonia and in 12 patients with aspiration pneumonia. Among patients with aspiration pneumonia, enteric gram-negative organisms were isolated in the patients with gastrointestinal disorders, whereas *S. pneumoniae* and *H. influenzae* predominated in those with community-acquired aspiration events. Only one anaerobic organism was found, and

the authors questioned the need for anaerobic coverage in both ventilator-associated pneumonia and aspiration pneumonia.<sup>28</sup>

Studies of the elderly continue to show the trend away from anaerobes. A study involving 95 institutionalized elderly patients with severe aspiration pneumonia reported 67 pathogens.<sup>29</sup> Gram-negative enteric bacteria accounted for 49% of the pathogens, anaerobes for 16%, and *S. aureus* for 12%. Aerobic gram-negative bacteria were found in conjunction with 55% of anaerobic isolates. Another study, involving 62 elderly hospitalized patients with aspiration pneumonia, showed that of 111 bacteria identified, gram-negative bacilli and anaerobes each accounted for 19.8% of the bacteria, and anaerobes and aerobes together were found in 66.7% of patients who died.<sup>30</sup> It is unclear why the pathogens have changed, but it may be due to a shift in the demographic characteristics of patients and earlier sampling today than in the past. Prior studies often collected cultures later in the illness, often after the development of empyema or lung abscess.<sup>1</sup> This discussion does not apply to chemical pneumonitis, which unlike aspiration pneumonia, is a noninfectious, inflammatory response of the airways and pulmonary parenchyma to acidic gastric contents or bile acids.<sup>1,31</sup>

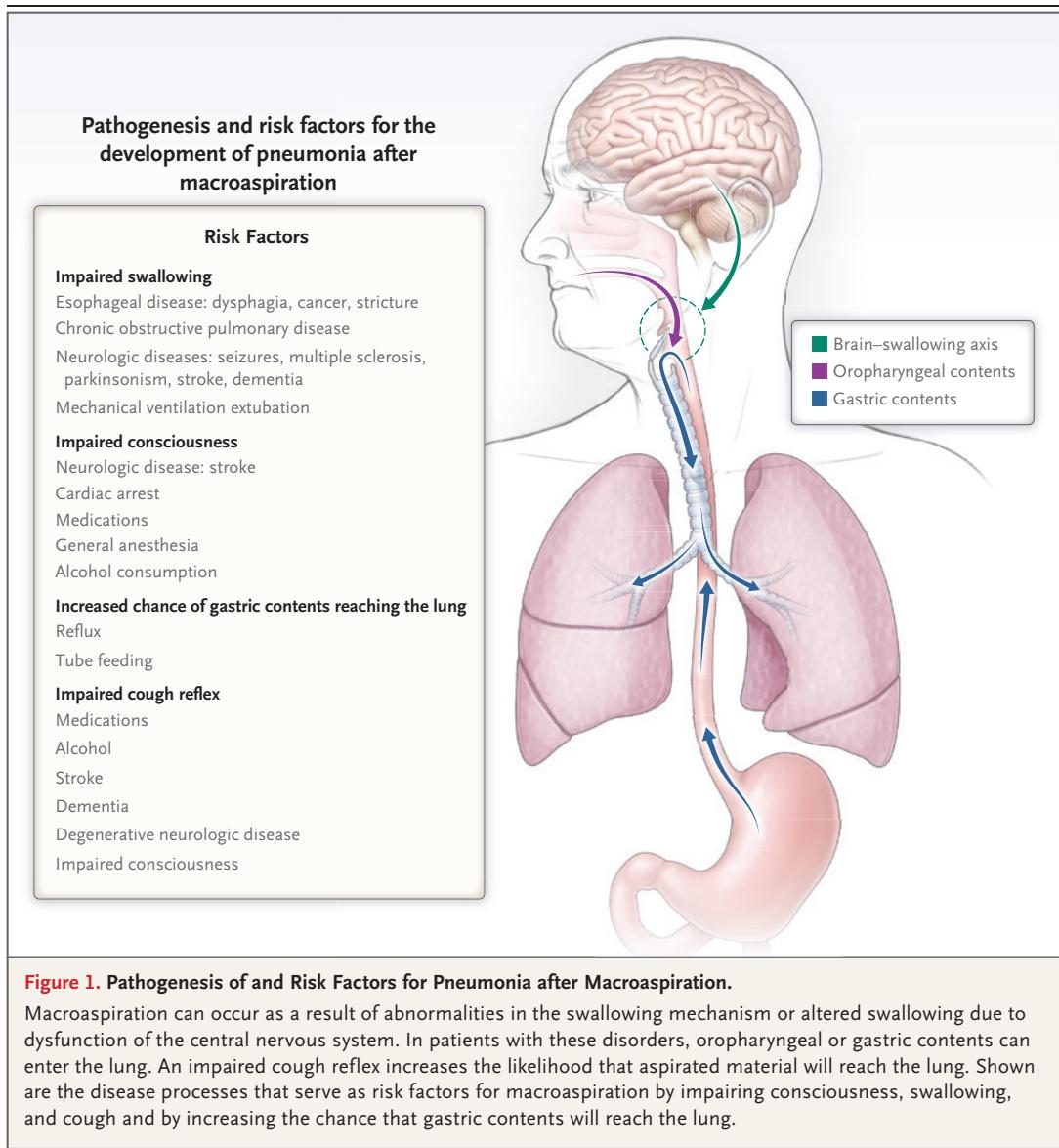
#### RISK FACTORS

Aspiration is often the result of impaired swallowing, which allows oral or gastric contents, or both, to enter the lung, especially in patients who also have an ineffective cough reflex (Fig. 1). Large-volume aspiration occurs with dysphagia; head, neck, and esophageal cancer; esophageal stricture and motility disorders; chronic obstructive pulmonary disease; and seizures.<sup>1,3,32-41</sup> In a case-control study involving elderly patients with pneumonia and healthy elderly controls, oropharyngeal dysphagia increased the risk of pneumonia (odds ratio, 11.9) and was present in nearly 92% of the patients who had pneumonia. Results of videofluoroscopic evaluation showed that 16.7% of the patients with pneumonia were able to swallow safely, as compared with 80% of the controls.<sup>32</sup> In extubated survivors of respiratory failure, dysphagia and aspiration are identified in at least 20% of patients. The frequency of swallowing dysfunction declines over time, but up to 35% of patients with swallowing dysfunction

at the time of extubation continue to have this problem at the time of discharge.<sup>33</sup>

Additional risks include degenerative neurologic diseases (multiple sclerosis, parkinsonism, and dementia) and impaired consciousness, particularly as a result of stroke and intracerebral hemorrhage, which can also impair cough clearance. The frequency of stroke-associated pneumonia is related to the severity of neurologic illness and its associated immune impairment, with higher rates among patients requiring intensive care than among those admitted to a stroke unit.<sup>34</sup> Impaired consciousness can also result from drug overdose and medications, including narcotic agents, general anesthetic agents, certain antidepressant agents, and alcohol (Fig. 2A). After adjustment for other risk factors, antipsychotic medications increased the risk of aspiration pneumonia by a factor of 1.5 in a study involving 146,552 hospitalized patients.<sup>35</sup> Enteral feeding can lead to high-volume aspiration, especially when associated with gastric dysmotility, poor cough, and altered mental status. In three studies of enteral feeding after a stroke in a total of more than 5000 patients, early tube feeding improved survival, as compared with no feeding, and in the first 2 to 3 weeks after the stroke, nasogastric tube feeding was associated with improved survival and functional outcomes, as compared with percutaneous enteral tube feeding.<sup>36</sup> Enteral feeding tubes are not currently recommended for patients with dementia.<sup>37</sup>

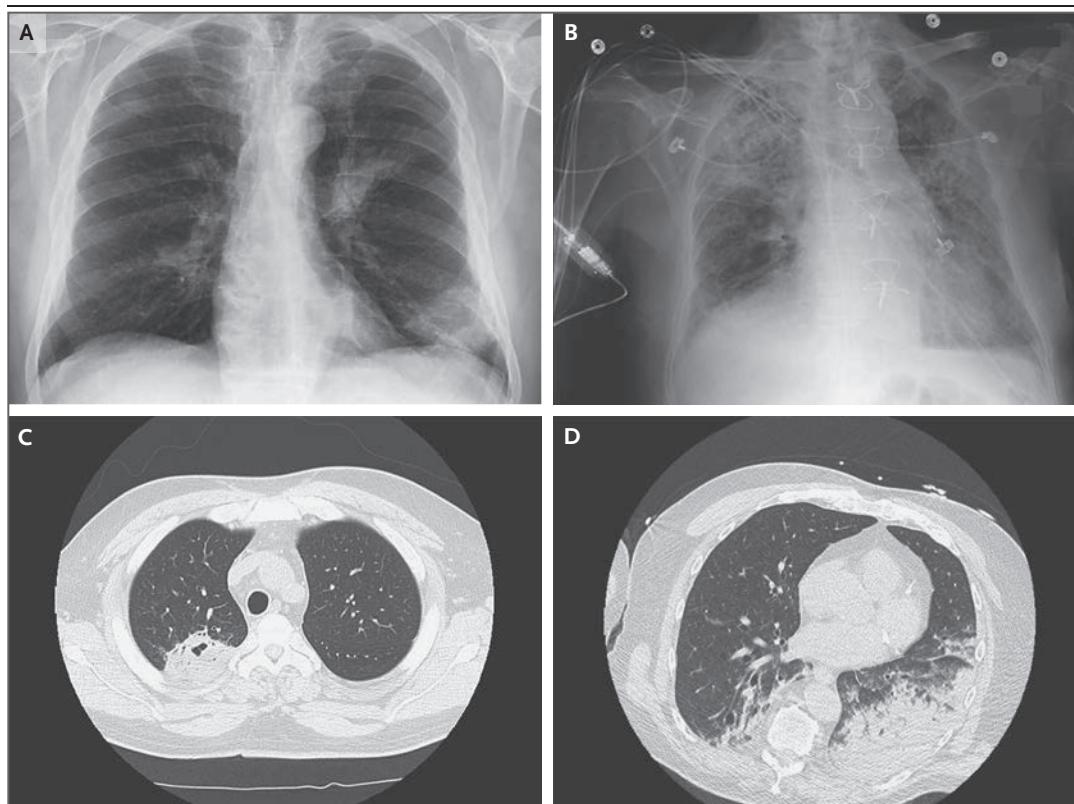
Patients with multiple risks have increased rates of aspiration pneumonia, death, and other adverse outcomes. A meta-analysis of studies involving frail elderly patients showed that dysphagia increased the odds ratio for aspiration pneumonia by a factor of 9.4, but when cerebrovascular disease was also present, the odds ratio rose to 12.9.<sup>38</sup> In a study involving 1348 patients with community-acquired pneumonia, 13.8% of the patients were considered to be at risk for aspiration, and this subgroup of patients had 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) as compared with the rest of the study population.<sup>39</sup> Similarly, a study involving 322 patients with community-acquired pneumonia 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).<sup>40</sup> 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. The relationship between distinct risk factors for macroaspiration and the frequency and outcome of aspiration pneumonia underscores the difference between aspiration pneumonia and traditional community-acquired pneumonia: patients with traditional community-acquired pneumonia have no associated increase in the risk of aspiration.

An important clinical context for aspiration

pneumonia is cardiac arrest. In a study involving 641 patients with cardiac arrest, pneumonia developed within 3 days after the event in 65% of the patients.<sup>41</sup> The presumed mechanism is aspiration of gastric contents during resuscitation (promoted by stomach ventilation and the resuscitation procedure) and inhalation of oral secretions during bag–valve–mask ventilation and intubation. When therapeutic hypothermia to 33°C was used after cardiac arrest, the odds ratio for early-onset pneumonia rose by a factor of 1.9.<sup>41</sup> However, a target temperature of 36°C may be associated with a lower risk of pneumonia.<sup>42</sup> Some studies showed that the incidence of early-



**Figure 2. Characteristic Imaging Findings in Patients with Aspiration Pneumonia.**

The chest radiograph in Panel A shows the findings in a 68-year-old man who presented with a several-week history of cough, blood in the sputum, and a 6.8-kg weight loss but who was otherwise in generally good health. He had extensive tooth decay and gingival inflammation. He did not drink alcohol or use illicit drugs but did take an antidepressant known to cause somnolence. The radiograph shows a cavitory infiltrate in the left lower lobe and an infiltrate in the left upper lobe. The radiograph in Panel B is from an 84-year-old man with small-bowel obstruction. He had repeated episodes of vomiting, with the development of bilateral lung infiltrates, respiratory failure, and the acute respiratory distress syndrome. Initial cultures were sterile, but 1 week later, he continued to have lung infiltrates and sputum culture showed methicillin-resistant *Staphylococcus aureus*. The computed tomographic (CT) scan in Panel C shows a cavitory infiltrate in the right upper lobe posteriorly in a 56-year-old man with cough after tooth extraction performed with local anesthesia. He drank four beers per day. Bronchoscopic cultures revealed *Klebsiella pneumoniae*. The CT scan in Panel D shows new bilateral infiltrates in posterior, gravity-dependent lung segments in a 79-year-old man with dyspnea after upper endoscopy complicated by vomiting.

onset pneumonia decreased among patients receiving systemic antibiotics at the time of cardiac arrest.<sup>43</sup> Two intervention studies involving comatose patients showed a benefit of administering prophylactic antibiotics for up to 24 hours after emergency intubation.<sup>44,45</sup>

#### CLINICAL FEATURES

Although macroaspiration is an essential feature of aspiration pneumonia and chemical pneumonitis, many episodes are unwitnessed; therefore, the magnitude of the exposure is often unknown.

Clinical features range from no symptoms to severe distress with respiratory failure, and the clinical consequences may develop acutely, subacutely, or slowly and progressively. Aspiration into the lung can affect either the airway (causing bronchospasm, asthma, and chronic cough) or the lung parenchyma. This discussion focuses on aspiration into the lung parenchyma, which can take the form of aspiration resulting in chemical pneumonitis, aspiration of bland material (blood or the contents of tube feeding), or aspiration resulting in bacterial pneumonia.

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. In a study involving patients with pneumonia who were more than 80 years of age, those with aspiration had a higher mortality, higher serum sodium levels, and worse renal function than patients without aspiration.<sup>46</sup> In a group of 53 patients with pneumonia and fluoroscopically documented dysphagia, more patients had bronchopneumonia than lobar pneumonia (68% vs. 15%), and 92% had posterior infiltrates.<sup>47</sup> Most patients with poor performance status had diffuse and not focal infiltrates. Aspiration pneumonia is associated with higher mortality than other forms of pneumonia acquired in the community (29.4% vs. 11.6%), a finding that may have implications for hospitals that do not properly code its presence.<sup>48</sup> In a survey of more than 1 million patients in more than 4200 hospitals, aspiration was documented in 4 to 26% of episodes of pneumonia. The expected mortality among patients with aspiration pneumonia is higher than that for other forms of pneumonia, and the risk-adjusted mortality (now used as a quality metric) is lower for hospitals reporting a high frequency of aspiration than for hospitals reporting a low frequency of aspiration.<sup>48</sup>

Macroaspiration of gastric contents can lead to chemical pneumonitis but only with large-volume, low-pH (usually <2.5) aspiration. In animal models, chemical pneumonitis develops only after exposure to at least 120 ml of gastric contents with a pH of 1. Described by Mendelson in 1946 as a consequence of obstetrical anesthesia, chemical pneumonitis is uncommon with modern anesthesia methods (1 case per 3216 procedures), with a higher risk during emergency surgery and a lower risk with elective procedures.<sup>49</sup> In up to 64% of patients with aspiration during anesthesia, clinical or radiographic abnormalities do not develop. Lung injury from acid aspiration is due to the release of inflammatory mediators, including chemokines (e.g., interleukin-8), proinflammatory cytokines (e.g., tumor necrosis factor), and neutrophil recruitment.<sup>50</sup>

Chemical 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, although the frequency rises if other risk factors (shock, trauma, or pancreatitis) are also present<sup>51</sup> (Fig. 2B). Low-pH aspirates are usually sterile, and bacterial infection is unusual initially, although superinfection may develop subsequently.

In most cases, neither chemical pneumonitis nor aspiration pneumonia occurs with tube feedings or aspirated blood, since the aspirate pH is usually high and uncontaminated by bacteria. Although acid-suppressing therapy is associated with an increased risk of community- or hospital-acquired pneumonia, which is related to gastric overgrowth by gram-negative bacteria, neutralization of gastric pH may reduce the risk of chemical pneumonitis.<sup>52</sup> In a prospective cohort study involving 255 patients undergoing gastrointestinal endoscopy, the use of proton-pump inhibitors or histamine H<sub>2</sub> blockers was associated with a significant reduction in the risk of gastric contents with a pH of <2.5 (odds ratio, 0.24).<sup>53</sup> Asphyxia may result if the aspirated volume of the bland material is large, but there may be few clinical findings if the volume is small. The chest radiograph may initially be abnormal, until the aspirated material is cleared by suction or coughing. In cases of unwitnessed aspiration, it may be difficult to distinguish among chemical pneumonitis, aspiration pneumonia, and aspiration of bland material. An aspirated solid foreign body can obstruct the airway and lead to postobstructive pneumonia, further complicating the distinction from bacterial pneumonia. In a series of patients with foreign-body aspiration who were more than 65 years of age, the event was recognized in only 29% of the patients, leading to a diagnostic delay of 1 to 3 months.<sup>54</sup> Chest radiographic findings were in the right lung in 65% of the patients, and food material accounted for more than 80% of the episodes.

## DIAGNOSIS

The diagnosis of aspiration pneumonia depends on a characteristic clinical history (witnessed macroaspiration), risk factors, and compatible findings on chest radiography. These radiographic findings include infiltrates in gravity-dependent lung 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) (Fig. 2C and 2D). However, a chest radiograph may be negative early in the course of aspiration pneumonia. In a study involving 208 patients with pneumonia (more than 60% of whom had aspiration), the chest radiograph was negative in 28% of patients in whom pneumonia was confirmed on computed tomography.<sup>55</sup> One of the entities that can be confused with aspiration pneumonia is negative-pressure pulmonary edema. It is important to consider this diagnosis, which is accompanied by bilateral and generally symmetric lung infiltrates and is the result of breathing against a closed airway after general anesthesia, choking, or near drowning, all conditions that may also be accompanied by aspiration.

Although the diagnosis is usually clinical, some studies have used quantitative lung-lavage cultures to distinguish bacterial from noninfectious (chemical and bland-aspiration) pneumonitis.<sup>56</sup> Several investigations have studied biomarker and biochemical measurements to predict bacterial infection after aspiration. A study involving 65 intubated patients with risk factors for aspiration and a new lung infiltrate correlated quantitative bronchoalveolar-lavage cultures with serum procalcitonin levels.<sup>56</sup> Measurement of procalcitonin levels on days 1 and 3 did not distinguish the 32 patients with culture-positive aspiration pneumonia from the 33 with culture-negative pneumonitis. In studies of ventilated patients, alpha-amylase levels (from salivary and pancreatic sources) were elevated in airway secretions, at a frequency reflecting the number of risk factors for aspiration, but the relevance of these findings to aspiration pneumonia and chemical pneumonitis is not certain, and this is not a method of value for diagnosis.<sup>57,58</sup>

## TREATMENT

### ASPIRATION PNEUMONIA

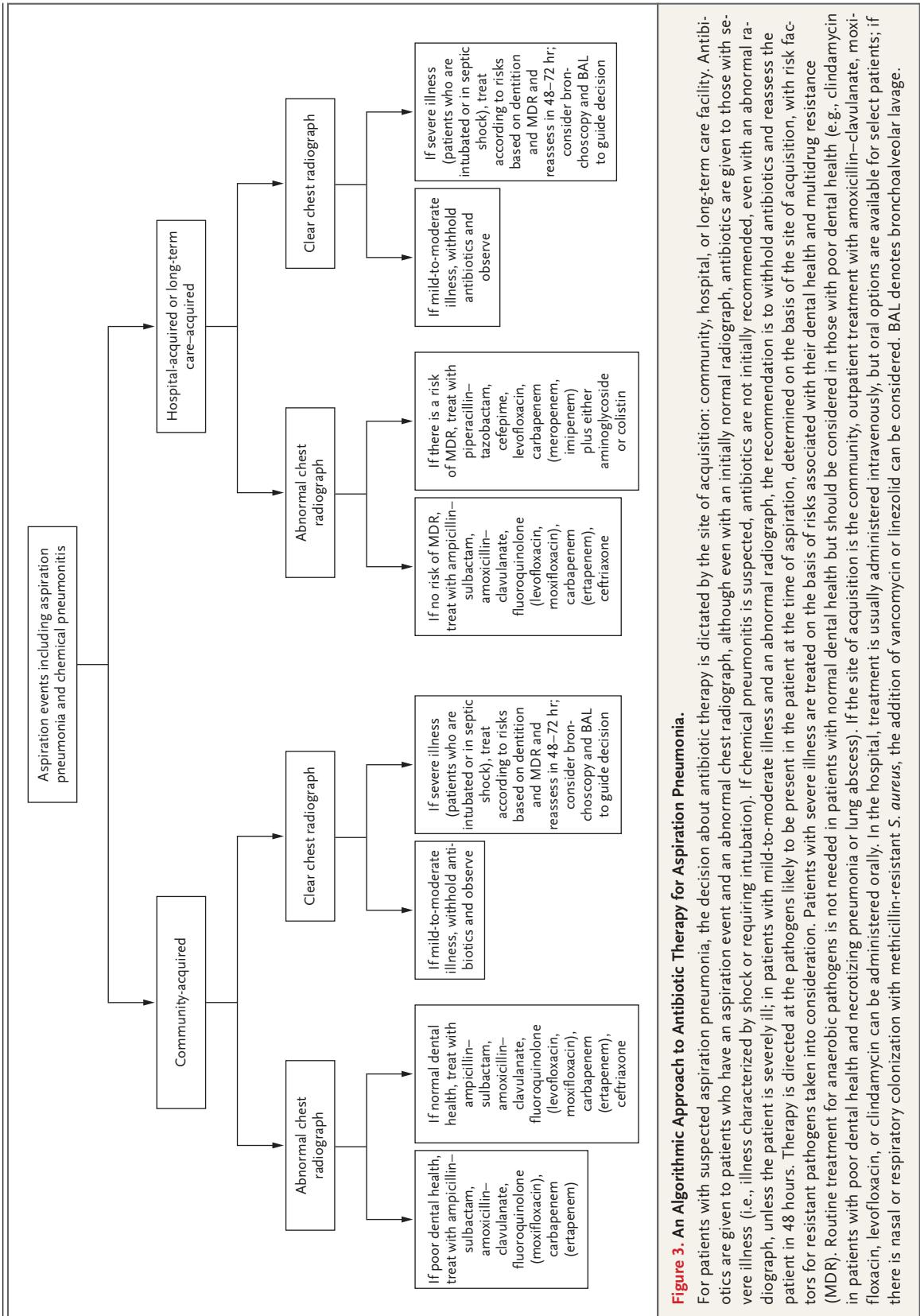
As documented pathogens have shifted from anaerobes to aerobes, treatment regimens have also evolved. Even when anaerobes predominated and penicillin was the drug of choice, penicillinase-producing anaerobes were reported.<sup>59,60</sup> Comparative studies of anaerobic lung abscess and necrotizing pneumonia showed the superiority of clindamycin, with penicillin failure attributed to resistant bacteroides species.<sup>61,62</sup> Treatment

with metronidazole failed in 5 of 11 cases of lung abscess and in a randomized trial was less effective than clindamycin for anaerobic pulmonary infection.<sup>63,64</sup>

A prospective, randomized trial showed no significant differences among ampicillin-sulbactam, clindamycin, and a carbapenem (panipenem-betamipron [not available in the United States]) for the treatment of suspected aspiration pneumonia in elderly Japanese patients.<sup>65</sup> A randomized trial involving 96 patients compared moxifloxacin with ampicillin-sulbactam; both regimens had clinical response rates of 66.7%.<sup>66</sup> Anaerobes were isolated in 29.6% of patients with only lung abscess. In those with only aspiration pneumonia, anaerobes were not found, and the most frequent aerobes were *Escherichia coli*, *Klebsiella pneumoniae*, and *P. aeruginosa* (Fig. 2C).

Antibiotic selection depends on the site of acquisition (the community, a hospital, or a long-term care facility) and risk factors for infection with multidrug-resistant pathogens. Risk factors include treatment with broad-spectrum antibiotics in the past 90 days and hospitalization for at least 5 days. For most patients with community-acquired cases, treatment with ampicillin-sulbactam, a carbapenem (ertapenem), or a fluoroquinolone (levofloxacin or moxifloxacin) is effective.<sup>3</sup> In such patients, we suggest adding clindamycin to another drug only when the risk of predominantly anaerobic infection is high, as it is for patients with severe periodontal disease and necrotizing pneumonia or lung abscess<sup>1</sup> (Fig. 3 and Table 1). With mixed infection, elimination of aerobic pathogens usually alters the local redox potential, eliminating anaerobes. For hospital-acquired cases with a low risk of multidrug-resistant pathogens, a similar regimen may be used. If resistance is a concern, broader-spectrum treatment with piperacillin-tazobactam, cefepime, levofloxacin, imipenem, or meropenem, either singly or in combination, is required<sup>67</sup> (Fig. 3 and Table 1). In cases of multidrug-resistant infection, an aminoglycoside or colistin may be used as part of a combination regimen, with the addition of vancomycin or linezolid if the patient has documented nasal or respiratory colonization with methicillin-resistant *S. aureus*.

In a recent study involving comatose, mechanically ventilated patients with aspiration, 43 of the 92 patients (46.7%) had bacterial aspiration pneumonia on the basis of bronchoscopic brush



**Figure 3. An Algorithmic Approach to Antibiotic Therapy for Aspiration Pneumonia.**

For patients with suspected aspiration pneumonia, the decision about antibiotic therapy is dictated by the site of acquisition: community, hospital, or long-term care facility. Antibiotics are given to patients who have an aspiration event and an abnormal chest radiograph, although even with an initially normal radiograph, antibiotics are given to those with severe illness (i.e., illness characterized by shock or requiring intubation). If chemical pneumonitis is suspected, antibiotics are not initially recommended, even with an abnormal radiograph, unless the patient is severely ill; in patients with mild-to-moderate illness and an abnormal radiograph, the recommendation is to withhold antibiotics and reassess the patient in 48 hours. Therapy is directed at the pathogens likely to be present in the patient at the time of aspiration, determined on the basis of the site of acquisition, with risk factors for resistant pathogens taken into consideration. Patients with severe illness are treated on the basis of risks associated with their dental health and multidrug resistance (MDR). Routine treatment for anaerobic pathogens is not needed in patients with normal dental health but should be considered in those with poor dental health (e.g., clindamycin in patients with poor dental health and necrotizing pneumonia or lung abscess). If the site of acquisition is the community, outpatient treatment with amoxicillin-clavulanate, moxifloxacin, levofloxacin, or clindamycin can be administered orally. In the hospital, treatment is usually administered intravenously, but oral options are available for select patients; if there is nasal or respiratory colonization with methicillin-resistant *S. aureus*, the addition of vancomycin or linezolid can be considered. BAL denotes bronchoalveolar lavage.

samples.<sup>68</sup> The investigators suggested that routine antibiotic treatment should be started only if bacterial infection is suspected but may be discontinued if bronchoscopic cultures are negative.

On the basis of data from studies of community-acquired pneumonia and hospital-acquired or ventilator-associated pneumonia, we suggest 5 to 7 days of treatment for patients with a good clinical response and no evidence of extrapulmonary infection, and longer treatment for those with necrotizing pneumonia, lung abscess, or empyema. In the case of lung abscess or empyema, drainage for diagnostic and treatment purposes may be needed. The choice of therapy should take into account potential drug-related adverse events, including *Clostridium difficile* colitis and selection of antibiotic resistance. More data are needed to identify the best antibiotic regimens for aspiration pneumonia and to determine the duration of treatment. No randomized, controlled trials have shown a role for glucocorticoids in the routine treatment of aspiration pneumonia, and we do not recommend their use.

#### CHEMICAL PNEUMONITIS

Initial treatment of gastric aspiration requires airway maintenance, management of airway edema or bronchospasm, and minimization of tissue damage. Depending on the severity of the pneumonitis and the extent of care required, treatment may include suctioning, bronchoscopy, intubation, mechanical ventilation, and intensive care. Routine adjunctive treatment with glucocorticoids is not recommended, and antibiotics are not needed routinely unless the patient is taking acid-suppressing medication or has small-bowel obstruction. In mild-to-moderate cases, we recommend withholding antibiotics even if there is radiographic evidence of an infiltrate, monitoring clinical and radiographic findings, and reassessing after 48 hours. In more serious cases, however, antibiotics should be started empirically, and the decision to continue antibiotic therapy for more than 2 to 3 days should be guided by the clinical course.

#### PREVENTION

Postoperative chemical pneumonitis can be minimized by ensuring that the patient has fasted for at least 8 hours and has abstained from clear liquids for at least 2 hours before surgery is per-

**Table 1. Antibiotic Treatment of Aspiration Pneumonia.\***

Drug	Dose, Schedule, and Route of Administration
Ampicillin–sulbactam	1.5–3 g every 6 hr, intravenous
Amoxicillin–clavulanate	875 mg twice daily, oral
Piperacillin–tazobactam	4.5 g every 8 hr or 3.375 g every 6 hr, intravenous
Ceftriaxone	1–2 g once daily, intravenous
Cefepime	2 g every 8–12 hr, intravenous
Ertapenem	1 g once daily, intravenous
Imipenem	500 mg every 6 hr or 1 g every 8 hr, intravenous
Meropenem	1 g every 8 hr, intravenous
Levofloxacin	750 mg once daily, intravenous or oral
Moxifloxacin	400 mg once daily, intravenous or oral
Clindamycin	450 mg three or four times daily, oral; or 600 mg every 8 hr, intravenous
Gentamicin or tobramycin†	5–7 mg/kg once daily, intravenous
Amikacin†	15 mg/kg once daily, intravenous
Colistin‡	9 million IU per day in two or three divided doses, intravenous
Vancomycin†	15 mg/kg every 12 hr, intravenous
Linezolid	600 mg every 12 hr, intravenous or oral

\* Doses are for patients with normal renal function.

† The dose should be adjusted to a trough level of less than 1 mg per liter for gentamicin and tobramycin, a trough level of less than 4 mg per liter for amikacin, and a trough level of 10 to 15 µg per milliliter for vancomycin, with renal function taken into consideration in all cases.

‡ A loading dose of 6 million to 9 million IU can be administered.

formed (Table 2). Medications known to promote aspiration and interfere with swallowing should be avoided, including sedatives, antipsychotic agents, and for some at-risk patients, antihistamines.<sup>35</sup> Aspiration-prevention efforts focusing on ventilator-associated pneumonia are not discussed here.

For patients with swallowing disorders, particularly after stroke, a full speech and swallowing evaluation is necessary. Efforts should be made to promote oral rather than enteral tube feeding, with the use of a mechanical soft diet with thickened liquids rather than pureed food and thin liquids. In addition, “nutritional rehabilitation” with swallowing exercises and early mobilization may help patients with dysphagia and may prevent recurrence of aspiration pneumonia.<sup>69</sup> Patients should receive enteral feeding in a semirecumbent rather than supine position to minimize the risk of gastric aspiration. For patients with oropharyngeal dysphagia, an effort

**Table 2. Prevention of Aspiration Pneumonia.****Recommended in the appropriate clinical setting**

Antibiotic therapy for 24 hr in comatose patients after emergency intubation  
 No food for at least 8 hr and no clear liquids for at least 2 hr before elective surgery with general anesthesia

**To be considered in the appropriate clinical setting**

Swallowing evaluation after stroke and after extubation from mechanical ventilation  
 Preference for angiotensin-converting-enzyme inhibitors for blood-pressure control after stroke  
 Oral care with brushing and removal of poorly maintained teeth  
 Feeding in a semirecumbent position for patients with stroke

**Not yet recommended; more data needed**

Swallowing exercises for patients with dysphagia after stroke  
 Oral chlorhexidine in patients at risk for aspiration

should be made to keep the patient's chin down and head turned to one side during feeding and to encourage swallowing of small volumes, multiple swallows, and coughing after each swallow.<sup>33</sup> In a study involving comatose patients, the risk of aspiration pneumonia was reduced by keeping patients in either the prone or semirecumbent position.<sup>70</sup>

The role of nasogastric tubes in preventing aspiration pneumonia is uncertain. In a study involving 1260 patients, the 630 patients with a nasogastric tube in place did not have more aspiration events during endoscopic observation of swallowing than the 630 patients without a nasogastric tube.<sup>71</sup> Postpyloric feeding is not superior to gastric feeding, and monitoring of postfeeding residual volume may not minimize the risk of aspiration.<sup>3,72</sup> For patients with stroke, particularly Asian patients, the use of angiotensin-converting-enzyme (ACE) inhibitors to control blood pressure can reduce the risk of aspiration pneumonia, possibly by elevating substance P levels, which promotes cough and improves the swallowing reflex.<sup>73,74</sup> In a meta-analysis of data from 8693 patients with stroke, patients who received ACE inhibitors had a reduced risk of aspiration, as compared with patients who did not receive ACE inhibitors (odds ratio, 0.6).<sup>74</sup> Cilostazol, an antiplatelet agent that may have a similar effect on substance P, has also been shown to prevent pneumonia after stroke.<sup>34</sup>

In the prevention of aspiration pneumonia, a focus on oral hygiene has yielded an inconsistent benefit, possibly because of study design issues.<sup>75</sup>

A meta-analysis of five randomized, controlled trials involving nonventilated patients at risk for aspiration pneumonia showed that oral care with chlorhexidine or mechanical oral cleaning was effective in preventing pneumonia (odds ratio, 0.4 to 0.6).<sup>76</sup> However, chlorhexidine use is controversial and may be associated with increased mortality among ventilated patients, possibly as a result of toxic effects if chlorhexidine is aspirated into the lung.<sup>77</sup> In a randomized study involving 252 patients, supplemental nutrition plus daily oral cleaning reduced the frequency of pneumonia (7.8%, vs. 17.7% with usual care;  $P=0.06$ ).<sup>78</sup> In a case-control study involving 539 patients undergoing surgery for esophageal cancer, postoperative pneumonia developed in 19.1% of the patients. Lack of preoperative oral care, including tooth scaling, mechanical cleaning, and tooth extraction if necessary, was an important risk factor.<sup>79</sup> Despite these promising findings, a cluster-randomized study involving 834 nursing home patients, with a mean observation time of slightly more than 1 year, showed no benefit of a comprehensive oral care program, which included manual tooth and gum brushing, chlorhexidine mouth washes, and upright positioning during feeding, with radiographic evidence of the development of pneumonia in 25% of the patients.<sup>80</sup>

Antibiotic administration for up to 24 hours in comatose patients who have been intubated on an emergency basis has shown a benefit in two trials. An open, randomized, controlled study involving 100 intubated, comatose patients with stroke or head injury showed that 1.5 g of cefuroxime given every 12 hours for two doses reduced the occurrence of pneumonia, particularly early-onset pneumonia.<sup>44</sup> Control patients receiving antibiotics at the time of intubation had lower pneumonia rates than those not receiving antibiotics. A subsequent cohort study showed that a single dose of antibiotic (ceftriaxone or ertapenem) administered within 4 hours after intubation was effective in preventing early-onset but not late-onset pneumonia in comatose patients,<sup>45</sup> including the 25% of patients who were intubated on an emergency basis after cardiac arrest.

**CONCLUSIONS**

Aspiration pneumonia is an important illness that is difficult to accurately diagnose and to

distinguish from other aspiration syndromes and community- and hospital-acquired pneumonias. The diagnosis should be considered in the appropriate clinical settings in patients with known risk factors for aspiration and characteristic clinical and radiographic findings. Aspiration pneumonia is treated with antibiotics as required but not with glucocorticoids. Preventive measures should be used for patients at risk for aspiration.

Dr. Mandell reports receiving fees for serving on a data monitoring committee from Bayer and Polyphor, fees for serving on a data and safety monitoring board from Cubist Pharmaceuticals and Shionogi, and lecture fees from Daiichi Sankyo; and Dr. Niederman, receiving consulting fees from Thermo Fisher, Paratek, Nabriva, Melinta, and Shionogi, advisory fees from Pfizer, and grant support and consulting fees from Merck and Bayer. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Dr. Robert P. Dickson, Division of Pulmonary and Critical Care Medicine, University of Michigan, for his assistance and thoughtful comments on an earlier version of the manuscript.

## REFERENCES

- Marik PE. Aspiration pneumonitis and aspiration pneumonia. *N Engl J Med* 2001; 344:665-71.
- Gleeson K, Eggl DF, Maxwell SL. Quantitative aspiration during sleep in normal subjects. *Chest* 1997;111:1266-72.
- DiBardino DM, Wunderink RG. Aspiration pneumonia: a review of modern trends. *J Crit Care* 2015;30:40-8.
- Boaden E, Lyons M, Singhrao SK, et al. Oral flora in acute stroke patients: a prospective exploratory observational study. *Gerodontology* 2017;34:343-56.
- Dickson RP, Erb-Downward JR, Huffnagle GB. The role of the bacterial microbiome in lung disease. *Expert Rev Respir Med* 2013;7:245-57.
- Segal LN, Rom WN, Weiden MD. Lung microbiome for clinicians: new discoveries about bugs in healthy and diseased lungs. *Ann Am Thorac Soc* 2014;11:108-16.
- Segal LN, Clemente JC, Tsay JC, et al. Enrichment of the lung microbiome with oral taxa is associated with lung inflammation of a Th17 phenotype. *Nat Microbiol* 2016;1:16031.
- Dickson RP, Erb-Downward JR, Falkowski NR, Hunter EM, Ashley SL, Huffnagle GB. The lung microbiota of healthy mice are highly variable, cluster by environment, and reflect variation in baseline lung innate immunity. *Am J Respir Crit Care Med* 2018;198:497-508.
- Casadevall A, Pirofski LA. The damage-response framework of microbial pathogenesis. *Nat Rev Microbiol* 2003;1:17-24.
- Casadevall A, Pirofski LA. Host-pathogen interactions: redefining the basic concepts of virulence and pathogenicity. *Infect Immun* 1999;67:3703-13.
- Dickson RP, Erb-Downward JR, Martinez FJ, Huffnagle GB. The microbiome and the respiratory tract. *Annu Rev Physiol* 2016;78:481-504.
- Dickson RP, Erb-Downward JR, Huffnagle GB. Towards an ecology of the lung: new conceptual models of pulmonary microbiology and pneumonia pathogenesis. *Lancet Respir Med* 2014;2:238-46.
- Dickson RP, Erb-Downward JR, Huffnagle GB. Homeostasis and its disruption in the lung microbiome. *Am J Physiol Lung Cell Mol Physiol* 2015;309:L1047-L1055.
- Marks LR, Davidson BA, Knight PR, Hakansson AP. Interkingdom signaling induces *Streptococcus pneumoniae* biofilm dispersion and transition from asymptomatic colonization to disease. *MBio* 2013; 4(4):e00438-13.
- Belay T, Sonnenfeld G. Differential effects of catecholamines on in vitro growth of pathogenic bacteria. *Life Sci* 2002;71:447-56.
- Freestone PP, Hirst RA, Sandrini SM, et al. Pseudomonas aeruginosa-catecholamine inotrope interactions: a contributory factor in the development of ventilator-associated pneumonia? *Chest* 2012;142:1200-10.
- Dewhirst FE, Chen T, Izard J, et al. The human oral microbiome. *J Bacteriol* 2010;192:5002-17.
- Aas JA, Paster BJ, Stokes LN, Olsen I, Dewhirst FE. Defining the normal bacterial flora of the oral cavity. *J Clin Microbiol* 2005;43:5721-32.
- Kageyama S, Takeshita T, Furuta M, et al. Relationships of variations in the tongue microbiota and pneumonia mortality in nursing home residents. *J Gerontol A Biol Sci Med Sci* 2018;73:1097-102.
- El-Solh AA, Pietrantonio C, Bhat A, et al. Colonization of dental plaques: a reservoir of respiratory pathogens for hospital-acquired pneumonia in institutionalized elders. *Chest* 2004;126:1575-82.
- Leibovitz A, Plotnikov G, Habor B, et al. Saliva secretion and oral flora in prolonged nasogastric tube-fed elderly patients. *Isr Med Assoc J* 2003;5:329-32.
- Johanson WG, Pierce AK, Sanford JP. Changing pharyngeal bacterial flora of hospitalized patients — emergence of gram-negative bacilli. *N Engl J Med* 1969; 281:1137-40.
- Bartlett JG, Gorbach SL, Finegold SM. The bacteriology of aspiration pneumonia. *Am J Med* 1974;56:202-7.
- Cesar L, Gonzalez C, Calia FM. Bacteriologic flora of aspiration-induced pulmonary infections. *Arch Intern Med* 1975; 135:711-4.
- Lorber B, Swenson RM. Bacteriology of aspiration pneumonia: a prospective study of community- and hospital-acquired cases. *Ann Intern Med* 1974;81:329-31.
- Bartlett JG. How important are anaerobic bacteria in aspiration pneumonia: when should they be treated and what is optimal therapy. *Infect Dis Clin North Am* 2013;27:149-55.
- Mier L, Dreyfuss D, Darchy B, 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.
- Marik PE, Careau P. The role of anaerobes in patients with ventilator-associated pneumonia and aspiration pneumonia: a prospective study. *Chest* 1999;115:178-83.
- El-Solh AA, Pietrantonio C, Bhat A, et al. Microbiology of severe aspiration pneumonia in institutionalized elderly. *Am J Respir Crit Care Med* 2003;167:1650-4.
- Tokuyasu H, Harada T, Watanabe E, et al. Effectiveness of meropenem for the treatment of aspiration pneumonia in elderly patients. *Intern Med* 2009;48:129-35.
- Wu YC, Hsu PK, Su KC, et al. Bile acid aspiration in suspected ventilator-associated pneumonia. *Chest* 2009;136:118-24.
- Almirall J, Rofes L, Serra-Prat M, et al. Oropharyngeal dysphagia is a risk factor for community-acquired pneumonia in the elderly. *Eur Respir J* 2013;41:923-8.
- Macht M, White SD, Moss M. Swallowing dysfunction after critical illness. *Chest* 2014;146:1681-9.
- Hannawi Y, Hannawi B, Rao CP, Suarez JI, Bershad EM. Stroke-associated pneumonia: major advances and obstacles. *Cerebrovasc Dis* 2013;35:430-43.
- Herzig SJ, LaSalvia MT, Naidus E, et al. Antipsychotics and the risk of aspiration pneumonia in individuals hospitalized for nonpsychiatric conditions: a cohort study. *J Am Geriatr Soc* 2017;65:2580-6.
- Dennis M, Lewis S, Cranswick G, Forbes J. FOOD: a multicentre randomised trial evaluating feeding policies in patients admitted to hospital with a recent stroke. *Health Technol Assess* 2006; 10:iii-iv, ix-x, 1-120.
- American Geriatrics Society Ethics Committee and Clinical Practice and Mod-

- els of Care Committee. American Geriatrics Society feeding tubes in advanced dementia position statement. *J Am Geriatr Soc* 2014;62:1590-3.
38. van der Maarel-Wierink CD, Vanobbergen 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.
39. 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.
40. Noguchi S, Yatera K, Kato T, 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.
41. Perbet S, Mongardon N, Dumas F, et al. Early-onset pneumonia after cardiac arrest: characteristics, risk factors and influence on prognosis. *Am J Respir Crit Care Med* 2011;184:1048-54.
42. Johnson NJ, Carlom DJ, Gaieski DF. Ventilator management and respiratory care after cardiac arrest: oxygenation, ventilation, infection, and injury. *Chest* 2018;153:1466-77.
43. Rello J, Diaz E, Roque M, Vallés J. Risk factors for developing pneumonia within 48 hours of intubation. *Am J Respir Crit Care Med* 1999;159:1742-6.
44. Sirvent JM, Torres A, El-Ebiary M, Castro P, de Batlle J, Bonet A. Protective effect of intravenously administered cefuroxime against nosocomial pneumonia in patients with structural coma. *Am J Respir Crit Care Med* 1997;155:1729-34.
45. Vallés J, Peredo R, Burgueño MJ, et al. Efficacy of single-dose antibiotic against early-onset pneumonia in comatose patients who are ventilated. *Chest* 2013;143:1219-25.
46. 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.
47. Komiya K, Ishii H, Umeki K, et al. Computed tomography findings of aspiration pneumonia in 53 patients. *Geriatr Gerontol Int* 2013;13:580-5.
48. Lindenauer PK, Strait KM, Grady JN, et al. Variation in the diagnosis of aspiration pneumonia and association with hospital pneumonia outcomes. *Ann Am Thorac Soc* 2018;15:562-9.
49. Warner MA, Warner ME, Weber JG. Clinical significance of pulmonary aspiration during the perioperative period. *Anesthesiology* 1993;78:56-62.
50. Raghavendran K, Nemzek J, Napolitano LM, Knight PR. Aspiration-induced lung injury. *Crit Care Med* 2011;39:818-26.
51. Gajic O, Dabbagh O, Park PK, et al. Early identification of patients at risk of acute lung injury: evaluation of lung injury prediction score in a multicenter cohort study. *Am J Respir Crit Care Med* 2011;183:462-70.
52. 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.
53. Phillips S, Liang SS, Formaz-Preston A, Stewart PA. High-risk residual gastric content in fasted patients undergoing gastrointestinal endoscopy: a prospective cohort study of prevalence and predictors. *Anaesth Intensive Care* 2015;43:728-33.
54. Lin L, Lv L, Wang Y, Zha X, Tang F, Liu X. The clinical features of foreign body aspiration into the lower airway in geriatric patients. *Clin Interv Aging* 2014;9:1613-8.
55. Miyashita N, Kawai Y, Tanaka T, et al. Detection failure rate of chest radiography for the identification of nursing and healthcare-associated pneumonia. *J Infect Chemother* 2015;21:492-6.
56. El-Solh AA, Vora H, Knight PR III, Porhomayon J. Diagnostic use of serum procalcitonin levels in pulmonary aspiration syndromes. *Crit Care Med* 2011;39:1251-6.
57. Weiss CH, Moazed F, DiBardino D, Swaroop M, Wunderink RG. Bronchoalveolar lavage amylase is associated with risk factors for aspiration and predicts bacterial pneumonia. *Crit Care Med* 2013;41:765-73.
58. Samanta S, Poddar B, Azim A, Singh RK, Gurjar M, Baronia AK. Significance of mini bronchoalveolar lavage fluid amylase level in ventilator-associated pneumonia: a prospective observational study. *Crit Care Med* 2018;46:71-8.
59. Bartlett JG. Treatment of anaerobic pleuropulmonary infections. *Ann Intern Med* 1975;83:376.
60. Finegold SM. Aspiration pneumonia. *Rev Infect Dis* 1991;13:Suppl 9:S737-S742.
61. Levison ME, Mangura CT, Lorber B, et al. Clindamycin compared with penicillin for the treatment of anaerobic lung abscess. *Ann Intern Med* 1983;98:466-71.
62. Gudiol F, Manresa F, Pallares R, et al. Clindamycin vs penicillin for anaerobic lung infections: high rate of penicillin failures associated with penicillin-resistant *Bacteroides melaninogenicus*. *Arch Intern Med* 1990;150:2525-9.
63. Sanders CV, Hanna BJ, Lewis AC. Metronidazole in the treatment of anaerobic infections. *Am Rev Respir Dis* 1979;120:337-43.
64. Perlino CA. Metronidazole vs clindamycin treatment of anaerobic pulmonary infection: failure of metronidazole therapy. *Arch Intern Med* 1981;141:1424-7.
65. Kadowaki M, Demura Y, Mizuno S, et al. Reappraisal of clindamycin IV monotherapy for treatment of mild-to-moderate aspiration pneumonia in elderly patients. *Chest* 2005;127:1276-82.
66. Ott SR, Allewelt M, Lorenz J, Reimnitz P, Lode H. Moxifloxacin vs ampicillin/sulbactam in aspiration pneumonia and primary lung abscess. *Infection* 2008;36:23-30.
67. Kalil AC, Metersky ML, Klompas M, 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(5):e61-e111.
68. Lascarrou JB, Lissonde F, Le Thuaut A, et al. Antibiotic therapy in comatose mechanically ventilated patients following aspiration: differentiating pneumonia from pneumonitis. *Crit Care Med* 2017;45:1268-75.
69. Momosaki R. Rehabilitative management for aspiration pneumonia in elderly patients. *J Gen Fam Med* 2017;18:12-5.
70. Adnet F, Borron SW, Finot MA, Minadeo J, Baud FJ. Relation of body position at the time of discovery with suspected aspiration pneumonia in poisoned comatose patients. *Crit Care Med* 1999;27:745-8.
71. Leder SB, Suiter DM. Effect of nasogastric tubes on incidence of aspiration. *Arch Phys Med Rehabil* 2008;89:648-51.
72. Elke G, Felbinger TW, Heyland DK. Gastric residual volume in critically ill patients: a dead marker or still alive? *Nutr Clin Pract* 2015;30:59-71.
73. Ohkubo T, Chapman N, Neal B, Woodward M, Omai 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.
74. 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.
75. Mylotte JM. Will maintenance of oral hygiene in nursing home residents prevent pneumonia? *J Am Geriatr Soc* 2018;66:590-4.
76. Kaneoka A, Pisegna JM, Miloro KV, et al. 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.
77. Klompas M, Speck K, Howell MD, Greene LR, Berenholtz SM. Reappraisal of routine oral care with chlorhexidine gluconate for patients receiving mechanical ventilation: systematic review and meta-analysis. *JAMA Intern Med* 2014;174:751-61.

78. Higashiguchi T, Ohara H, Kamakura Y, et al. Efficacy of a new post-mouthwash intervention (wiping plus oral nutritional supplements) for preventing aspiration pneumonia in elderly people: a multicenter, randomized, comparative trial. *Ann Nutr Metab* 2017;71:253-60.
79. Soutome S, Yanamoto S, Funahara M, et al. Effect of perioperative oral care on prevention of postoperative pneumonia associated with esophageal cancer surgery: a multicenter case-control study with propensity score matching analysis. *Medicine (Baltimore)* 2017;96(33):e7436.
80. Juthani-Mehta M, Van Ness PH, McGloin J, et al. A cluster-randomized controlled trial of a multicomponent intervention protocol for pneumonia prevention among nursing home elders. *Clin Infect Dis* 2015;60:849-57.

Copyright © 2019 Massachusetts Medical Society.

#### IMAGES IN CLINICAL MEDICINE

The *Journal* welcomes consideration of new submissions for Images in Clinical Medicine. Instructions for authors and procedures for submissions can be found on the *Journal's* website at [NEJM.org](http://NEJM.org). At the discretion of the editor, images that are accepted for publication may appear in the print version of the *Journal*, the electronic version, or both.