
REVIEW

This paper is dedicated to the 70th anniversary of the founding of Physiologia Bohemoslovaca (currently Physiological Research)

Aspiration Syndromes and Associated Lung Injury: Incidence, Pathophysiology and Management

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Summary

Aspiration is a common condition affecting healthy or sick patients which could create an acute or chronic inflammatory reaction in the lungs. Aspiration syndromes could be categorized according to a content entering the respiratory system into bacterial aspiration pneumonia with the gastric or oropharyngeal bacteria entering, aspiration chemical pneumonitis with bacteria-free gastric acid aspiration, or aspiration of a foreign body which causes an acute pulmonary emergency. There are differences in the clinical presentation of volume-dependent aspirations (microaspiration and macroaspiration): the higher is the volume of aspiration, the greater is the injury to the patient and more serious are the health consequences (with 70 % mortality rate for hospitalized patients). Aspiration syndromes can affect both the airways and pulmonary parenchyma, leading to acute lung injury, increased hospitalization rate and worse outcomes in critically ill patients. Impaired alveolar-capillary permeability, oedema formation, neutrophilic inflammatory response and pulmonary surfactant inactivation lead to reduced lung compliance and loss of aerated lung tissue and give rise to hypoxemia and respiratory failure. This review discusses the effect of aspiration events on the pulmonary tissue. The main focus is to distinguish the differences between bacterial and chemical pneumonia, their clinical presentation and symptoms, risk factors of developing the changes, possibilities of diagnostics and management as well as prevention of aspirations. Because of a risk of serious lung damage after the aspiration, pathophysiology and processes leading to lung tissue injury are discussed in detail. Data sources represent a systematic literature search using relevant medical subject headings.

Key words

Aspiration syndromes • Aspiration pneumonitis • Aspiration pneumonia • Acute lung injury • Pathophysiology

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Introduction

Aspiration represents a great danger for patients. In aspiration, a material, either liquid or even a foreign object passes from the mouth or the upper part of the gastrointestinal tract into the lungs. Aspiration syndromes occur more frequently than reported, in many cases, the disease is not recognized (unwitnessed). Aspiration symptoms are classified based on three main characteristics: infectiousness of the inoculum, its volume, and acuity of the onset of the clinical syndrome (Son *et al.* 2017).

Aspiration pneumonitis and aspiration pneumonia are two important manifestations of macroaspiration that cause abrupt changes in the patients' conditions (Marik 2001). The most affected are hospitalized and critically ill patients where the mortality rate could be 70 % in large volume and low pH aspirates (DeLegge 2002, DiBardino and Wunderink 2015). The aspiration syndromes can be difficult to distinguish. Clinical presentation and disease management are

affected by various variables, such as bacterial virulence, risk of repeated events, and the site of acquisition (nursing home, hospital, or community) (Mandell and Niederman 2019). They also differ in terms of providing the appropriate treatment for each of the conditions. In addition, aspiration syndromes are recognized as an independent risk factor for the subsequent development of acute respiratory distress syndrome (ARDS), a life-threatening condition characterized by diffuse lung damage, inflammation, oedema formation, and surfactant dysfunction leading to respiratory failure (Mokrá 2020, Raghavendran and Napolitano 2011, Zaloga 2002).

We systematically searched NCBI, Scopus, Web of Science, and Cochrane Library databases of 'aspiration pneumonia, aspiration pneumonitis, ARDS, acute lung injury' from inception to 14 July 2021. Data sources included scientific reviews and original research publications from the human and veterinary literature. All reviews and studies that added some information to the understanding of aspiration syndromes were included. Finally, we aimed to summarize a current evidence surrounding the clinical presentation, pathophysiology, diagnosis, treatment, risks and prevention of aspiration syndromes.

Pulmonary aspiration syndromes

Pulmonary aspiration, which is defined as the

misdirection of oropharyngeal or gastric contents into the larynx and lower respiratory tract, can be a dangerous phenomenon (Marik 2001). Various materials can be aspirated, such as bacteria, nasal secretions or saliva, toxic substances, liquids and food, or gastric contents (Son *et al.* 2017, Zaloga 2002). Aspiration syndrome occurs more frequently than is recorded, and the disease is often misdiagnosed. In hospitalized and institutionalized patients with predisposing disorders, early detection of this complication and efficient preventive measures will considerably minimize the severity of health complications and mortality associated with aspiration syndromes (Petroianni *et al.* 2006). Aspiration syndrome may occur due to (1) airway syndromes such as chronic cough, exacerbation of asthma/bronchospasm or bronchiolitis obliterans in lung transplantation, (2) lung parenchymal syndromes such as exacerbation of fibrotic lung disease or aspiration pneumonitis, (3) bacterial pneumonia such as community or hospital-acquired, ventilator-associated or aspiration pneumonia (Son *et al.* 2017). However, only bacterial types of pneumonia and acute circumstances are infectious. The summary is shown in Table 1.

There are three particular classifications of aspiration syndromes that are pathologically and clinically distinct: (1) Foreign body aspiration (FBA), (2) Aspiration pneumonitis, (3) Aspiration pneumonia (Paintal and Kushner 2007).

Table 1. Aspiration syndromes (adapted from Sun *et al.* 2017).

	Infectious inoculum	Volume	Acuity of onset
<i>AIRWAY SYNDROMES</i>			
• <i>Chronic cough</i>	No	Micro	Chronic
• <i>Exacerbation of asthma/bronchospasm</i>	No	Micro	Acute/subacute
• <i>Bronchiolitis obliterans in lung transplantation</i>	No	Micro	Chronic
<i>LUNG PARENCHYMAL SYNDROMES</i>			
• <i>Exacerbation of fibrotic lung disease</i>	No	Micro	Chronic
• <i>Aspiration pneumonitis</i>	No	Macro	Acute
<i>BACTERIAL PNEUMONIA</i>			
• <i>Community-acquired</i>	Yes	Micro	Acute
• <i>Hospital-acquired</i>	Yes	Variable	Acute
• <i>Ventilator-associated</i>	Yes	Micro	Acute
• <i>Aspiration pneumonia</i>	Yes	Macro	Acute

Foreign body aspiration

Infants and toddlers are most likely to suffer from the foreign body aspiration (FBA) which mechanically blocks the airways and causes asphyxiation (Marraro *et al.* 2007, Paintal and Kushner 2007). In adults, higher risk of foreign body asphyxiation syndrome may be observed in patients with impaired sensory capacities, craniofacial trauma, loose teeth, or dental appliances (Umesan *et al.* 2012). The typical presentation of tracheobronchial blockage resulting from aspiration includes a history of eating or swallowing followed by an abrupt onset of difficult speaking or breathing.

Common signs and symptoms of FBA include tachypnoea, tachycardia, wheezing, cough, and cyanosis (Paintal and Kushner 2007). The Heimlich manoeuvre is used to manage foreign object asphyxiation (Montana *et al.* 2020) or the other procedures should be rapidly used to clear the airways. This is an urgent situation because in complete blockade of the trachea, there are only 3 to 5 minutes to restore the airway, otherwise there is a risk of ischemia damage to the brain, heart, and other essential organs that cannot be reversed (Stubington and Kamani 2021). Treatment options represent an extraction of the foreign object using a rigid bronchoscope or flexible fiberoptic laryngoscope (Ibrahim Sersar *et al.* 2005, Rafanan and Mehta 2001).

FBA is a rare but potentially fatal complication that occurs in 0.16–0.33 % of adult bronchoscopic procedures (Sehgal *et al.* 2015), and is slightly more common in males (Limper and Prakash, 1990, Sehgal *et al.* 2015). The vast majority of adult patients with FBA has obvious risk factors for aspiration including neurological deficits with swallowing difficulties or altered mental status, neuromuscular disease, intoxication, or has an iatrogenic cause. Adult FBA typically presents with choking followed by persistent coughing, but when the first event goes unnoticed, it might mimic more chronic diseases such as COPD, asthma, and obstructive pneumonia (Boyd *et al.* 2009, Limper and Prakash 1990, Lin *et al.* 2014, Sehgal *et al.* 2015). Wheezing, dyspnea, hemoptysis, chest discomfort, and recurrent pneumonia are some of the less common symptoms. The size of the FB and the area in which it becomes lodged define the symptoms. Impaction in the trachea leads to a more dramatic presentation of inspiratory stridor with frequent coughing, while occlusion of the lower bronchi can result in coughing, wheezing, dyspnea, or hemoptysis, and may be mistaken with an alternative diagnosis (Dikensoy *et al.* 2002).

Aspiration pneumonitis

Aspiration pneumonitis is defined as an acute lung injury (ALI) caused by macroaspiration of refluxed gastric contents (Son *et al.* 2017). Aspiration of gastric contents causing a chemical pneumonitis characterized by fever, cyanosis, hypoxia, pulmonary oedema, and potential death was initially described as “Mendelson syndrome” (Salik and Doherty 2021). However, the contents of the stomach include not only acidic fluid but also food particles. Animal experiments showed that administration of small non-acidified gastric particles (SNAP) into the trachea induced acute neutrophilic lung inflammation within 4 to 6 hours, without any direct lung injury in the early phases (Knight *et al.* 1993). However, the combination of SNAP and acid was found to be in close resemblance to the gastric aspiration, with more severe changes observed in comparison with lung injuries due to acid or SNAP alone (Davidson *et al.* 2005, Son *et al.* 2017).

The gastric contents are sterile under normal conditions. However, the change in gastric fluid pH creates an environment in which the potentially pathogenic microorganisms become viable. For instance, gram-negative bacteria may cause a gastric colonization in patients who are fed enterally, in patients with gastroparesis or with small-bowel blockage [47, 48]. When gastric aspiration occurs in those circumstances, a lung infection may develop as a result of the bacteria present in the gastric contents, indicating how pneumonitis can overlap with aspiration pneumonia (Son *et al.* 2017).

The pathophysiology of aspiration pneumonitis. The majority of aspirates in the clinical scenarios are liquid whereas the extent and progression of the injury to the pulmonary parenchyma are determined by the nature of the aspirate. The inflammation is a result of the chemical burn assuring to the mucosa of the trachea, bronchi and parenchyma of the lungs, due to the toxicity of pH of the gastric aspirate (Hunt *et al.* 2018). While in normal conditions, macrophages are important in the first defence line, the acidic environment of the stomach decreases activity of the macrophages. This further reduces a bacterial destruction and increases a risk of developing aseptic respiratory tract infections after gastric content aspiration, (Heming *et al.* 2001).

Generally, two clinical phases of pneumonitis can be distinguished (Raghavendran *et al.* 2011). The first phase is defined by intense coughing or

bronchospasm that occur immediately after the aspiration incident, characterized by stimulation of capsaicin-sensitive neurons and direct caustic actions of low pH on airway epithelium. The second phase is characterized by the onset of neutrophil-induced pulmonary inflammation during the next 4–6 hours (Kennedy *et al.* 1989). The longer is the acidic content in contact with the respiratory tract, the more potent is the alteration of the immune system (Hackett *et al.* 2016). Exposure to low pH of gastric content leads to a loss of pulmonary microvascular integrity, resulting in fluid and protein extravasation into the airways and alveoli (Raghavendran *et al.* 2011). Plasma proteins and other components of oedema fluid can directly interfere with the function of alveolar surfactant what increases the breathing effort due to increased airway resistance and decreases a diffusion of oxygen.

Gastric aspiration triggers an inflammatory cellular response. Low pH-mobilized and activated neutrophils release histamine, leukotrienes and TGF- β which affect the surfactant integrity of the alveoli and contribute to respiratory insufficiency (Reeves *et al.* 2002). There have been several local and systemic inflammatory mediators identified to have a role in acid-induced lung injury (Goldman *et al.* 1993). Specifically levels of proximal proinflammatory cytokine, tumor necrosis factor (TNF)- α (Davidson *et al.* 1999), neutrophil chemotactic chemokine interleukin (IL)-8 (Folkesson *et al.* 1995), macrophage inflammatory protein-2 (MIP-2) (Shanley *et al.* 2000) and cytokine-induced neutrophil chemoattractant-1 (CINC-1) are elevated in the bronchoalveolar lavage (BAL) fluid (Knight *et al.* 2004). In addition, increases in leukocyte-derived oxidants and proteinases (Raghavendran *et al.* 2011) and activation of complement participate in the systemic response of acid-induced lung injury (Nishizawa *et al.* 1996). Besides epithelial damage, neutrophils themselves cause endothelial cell injury via inhibition of NADPH oxidase. Both pepsin and bile salts also activate the effect of IL-8 causing a direct damage, and *via* stimulation of neutrophilic influx induce an endothelial cell injury (Brinkmann *et al.* 2004).

Dysfunction of pulmonary surfactant in acid aspiration pneumonia was confirmed in experiments where treatment with exogenous surfactant improved a pulmonary function, but only when inhibitory plasma proteins were removed by a lavage (Davidson *et al.* 2005, Eijking *et al.* 1993).

Aspiration pneumonia

Aspiration pneumonia is a process of proliferation and invasion of pulmonary parenchyma caused by the inhalation of oropharyngeal secretions that are colonized by pathogenic bacteria (Almirall *et al.* 2021). Pneumonia can be induced by aspiration of infectious content from the upper airways or the oral cavity, or in more serious cases the bacteria can enter the lungs via hematogenous spread from other locations (Cabre *et al.* 2010).

While previously the most prominent types of bacteria present in aspiration pneumonia were the anaerobic bacteria (Mandell and Niederman 2019), nowadays there has been a shift in the observed types of microorganisms (Bartlett, 2013). Main types of bacteria in a community-acquired pneumonia are *Streptococcus Pneumoniae*, *Staphylococcus Aureus*, *Haemophilus Influenza*, and *Enterobacteria*, whereas a hospital-acquired pneumonia is usually caused by gram-negative enteric bacteria, such as *Pseudomonas Aeruginosa* (Rotstein *et al.* 2008). In patients suffering from gastrointestinal disorders, the gram-negative *Enterococci* are often detected (Mandell and Niederman 2019). However, in small burden of bacteria in the oropharyngeal secretion, good coughing mechanisms along with the patient's cellular and humoral immune systems, and active ciliary clearance, may prevent an infection of the lung after the aspiration. Nevertheless, any impairment of these mechanisms accompanied by abundant aspiration may result in aspiration pneumonia (Dickson *et al.* 2013).

The pathophysiology of aspiration pneumonia cannot be understood in the absence of bacteriological investigation. It's critical to distinguish aseptic aspiration pneumonitis, in which the damage to the pulmonary tissue is caused by acidic gastric material rather than bacteria, from bacterial aspiration pneumonia (Mandell and Niederman 2019). In addition, varying frequency, volume, and particle size result into a wide array of changes, which are similar to the pathophysiology of ARDS (Neill and Dean 2019).

The microbiological aetiology of aspiration pneumonia may depend on different aspects. For instance, the type of pathogen in community-acquired pneumonia is influenced by age, smoking habits, alcohol abuse, and comorbidities such as COPD, diabetes mellitus, liver disease, renal failure, and neurological illness (Almirall *et al.* 2021, Liapikou *et al.* 2014).

Chronic and frequent aspiration contributes to pneumonia because of denuded epithelium and increased pool of bacteria in the lungs (Neill and Dean, 2019).

The pathophysiology of aspiration pneumonia can be explained as the combination of risk factors that alter swallowing function, cause aspiration, and predispose the oropharynx to bacterial colonization (Ortega Fernández and Clavé 2013). The pathological changes occur when the normal defense mechanisms, i.e. the mucociliary transport and alveolar macrophages acting in clearing microaspirations, fail in a predisposed individual. Entrance of aspirate with common flora organisms from the oropharynx and oesophagus into the bronchi and alveolar space triggers the production of proinflammatory cytokines, TNF- α , and interleukins (Sanivarapu and Gibson 2021).

Aspiration syndromes are recognized as an independent risk factor for the subsequent development of ARDS (Mokrá, 2020, Raghavendran *et al.* 2011, Son *et al.* 2017). Macrophages, alveolar cells, immune effector cells, and neutrophils, as well as platelets and monocytes are critical in defending the lung and play key roles in acute lung injury (ALI) induced by aspiration syndromes (Matthay *et al.* 2019).

The lung injury is associated with an accumulation of protein-rich oedema fluid in the interstitium and the distal air spaces (Fanelli *et al.* 2013). Conceptually, increasing lung vascular permeability can occur because of a breakdown of endothelial junctions or a death of endothelial cells. Endothelial cell activation results to generation of mediators, such as angiotensin-2, and leukocyte accumulation. Endothelial cell activation results into neutrophil-platelet interaction. Neutrophil-platelet aggregates seem to play a synergistic role in causing an increase in lung vascular permeability to protein (Huppert *et al.* 2019, Kosutova *et al.* 2019). Migration and activation of neutrophils into the lung lead to subsequent degranulation and release of toxic mediators, such as proteases, reactive oxygen and nitrogen species, pro-inflammatory cytokines, and pro-coagulant molecules (Mikolka *et al.* 2021, 2019). This causes diffuse inflammatory reaction, pulmonary surfactant inactivation, and reduced lung compliance. Ventilation-perfusion mismatch and increased physiological dead space give rise to hypoxemia, which further affects a lung function in the early phase after aspiration (Kane-Gill *et al.* 2007).

Risk factors of aspiration syndromes

When aspiration occurs, two specific factors have been identified as causal: (1) lost or reduced protective reflexes when the individual's consciousness has undergone ageing-related alteration, (2) impairments of neuromuscular function (Marik and Kaplan, 2003). There are additional contributing factors that put the older adult at risk for aspiration, including use of sedatives, drug abuse, dementia, use of alcohol, metabolic disorders, traumatic brain injury, stroke, seizures and any type of therapeutic or diagnostic procedures that involve the upper thorax or the oesophagus (Huxley *et al.* 1978, Langmore *et al.* 1998, Marik and Kaplan 2003).

The clinical signs of an aspiration incident range from subclinical symptoms like dry cough or dysphonia to life-threatening disorders such as ARDS. Secondary infection, lung abscess, airway obstruction, exogenous lipid pneumonia, and progression into chronic interstitial fibrosis can all aggravate the pathogenic process (Marik 2001). Patients with low gastric pH, decreased gastroesophageal sphincter tone, or elevated gastric pressure are also at risk, as well as the other predisposing factors such as sepsis, pregnancy, and nutrition (Raghavendran *et al.* 2011).

The risk factors for aspiration of a large volume are: (1) altered state of consciousness: sedation, traumatic brain injury, encephalopathy, seizure disorder, poisoning, alcohol/drug intoxication, (2) gastrointestinal disorders: gastroesophageal reflux, gastroparesis, bowel obstruction/ileus, oesophageal motility disorders: primary – achalasia, oesophageal stricture, secondary – scleroderma, polymyositis, (3) compromised gag reflex: endotracheal intubation, bulbar paralysis, enteral tube feeding, (4) dysphagia/swallowing dysfunction: stroke, dementia, chronic obstructive pulmonary disease (COPD), Parkinson's disease, (5) obesity, and (6) labor (Raghavendran and Napolitano 2011, Son *et al.* 2017). Risk factors for aspiration syndromes are listed in Table 2.

Microaspiration and macroaspiration

The amount of aspirated material also belongs to the risk factors for aspiration. Microaspiration represents smaller amounts of reflux material when the microbes are seeded into the lower airways most often in the form of oropharyngeal secretions. It occurs even in healthy individuals and to cause a disease, it requires

a compromise in the defensive systems (Segal *et al.* 2014). Higher prevalence of microaspiration may be found in asthma, COPD, sleep apnea of the obstructive type, atypical lung infections and cystic fibrosis (CF) where along with an acid reflux the coordination of breathing and swallowing (Miller *et al.* 2005) and clearance of microorganisms from the lower airways (Randell and Boucher 2006) are reduced.

Table 2. Risk factors for aspiration syndromes

ALTERED STATE OF CONSCIOUSNESS
<ul style="list-style-type: none"> • Sedation • Traumatic brain injury • Encephalopathy • Seizure disorder • Poisoning • Alcohol/drug intoxication
GASTROINTESTINAL DISORDERS
<ul style="list-style-type: none"> • Gastroesophageal reflux • Gastroparesis • Bowel obstruction/ileus • Oesophageal motility disorders <ul style="list-style-type: none"> - Prim: Achalasia, Esophageal stricture - Sec: Scleroderma, Polymyositis
COMPROMISED GAG REFLEX
<ul style="list-style-type: none"> • Presence of endotracheal intubation • Bulbar paralysis • Enteral tube feeding
DYSPHAGIA / SWALLOWING DYSFUNCTION
<ul style="list-style-type: none"> • Stroke • Parkinson's disease • Dementia • Chronic obstructive pulmonary disease
OBESITY
LABOUR

Macroaspiration occurs when a large volume of particles is inhaled into the lungs, most commonly after impairment of protective reflexes, e.g., in neurodegenerative diseases or drug overdose (Son *et al.* 2017). Macroaspiration can also occur as a result of aberrant swallowing mechanics or when swallowing is hampered by CNS dysfunction, allowing stomach or oesophageal contents to enter the lungs. Increased risk of

macroaspiration have been also linked to dementia and taking of sleeping pills (Mandell and Niederman 2019). Development of aspiration pneumonia is a frequent consequence of cardiopulmonary resuscitation due to cardiac arrest, in which the gastric content may enter the lungs. Pneumonia developed within 3 days after the event in 65 % of the patients (Perbet *et al.* 2011). In addition, larger volume aspiration can occur when a patient has cancer of the neck, head, or oesophagus, dysphagia, or limited motility of the oesophagus, or in COPD or seizures (Mandell and Niederman 2019).

Macroaspiration could result into ALI (Mokrá, 2020). The severity of clinical presentation of macroaspiration and microaspiration differs according to aspirated volume so that higher is the volume of the aspiration, the greater is the injury to the patient and the more serious are the health consequences (Neill and Dean 2019). Bacterial pneumonia as a secondary impact was developed in 25 % of patients who had macroaspiration and pneumonitis. However, only some therapies can be used for treating macroaspiration. Antibiotic therapy given when aspiration pneumonia is apparent after a macroaspiration event was found to be more efficacious than prophylactic antimicrobial therapy in individuals with acute aspiration pneumonitis (Dragan *et al.* 2018, Kane-Gill *et al.* 2007). This knowledge allow the specialists to spend less time implementing the wrong treatment based on the situation being assessed (Grieco *et al.* 2021).

Incidence and epidemiology of aspiration syndromes

Most aspiration events go undetected or unnoticed, as it is difficult to suggest commonness and abundance of pneumonia caused by aspiration, both micro and macro-aspiration. In up to 64 % of aspirations during anaesthesia, clinical or abnormal radiological signs were not detected (Raghavendran *et al.* 2011). There are a few studies available describing an aspiration as a cause of community-acquired pneumonia. Aspiration pneumonia accounts for 5 to 15 % of cases of community-acquired pneumonia (Marik 2001), however, data on hospital-acquired pneumonia is unavailable (Mandell and Niederman 2019). Aspiration was found in 4 to 26 % of pneumonia episodes in a survey of more than 1 million patients in more than 4200 hospitals.

Patients with aspiration pneumonia have higher predicted mortality than those with other types of pneumonia, and a risk-adjusted mortality, used as

a quality metric, is lower in hospitals reporting a high frequency of aspiration than in hospitals reporting a low frequency of aspiration (Lindenauer *et al.* 2018). General anesthesia is a well-known reason for gastric aspiration that affects one out of every two to three thousand patients (Marik 2001, Raghavendran *et al.* 2011, Warner *et al.* 1993). In reality, it has been observed that aspiration occurs in roughly 3 out of every 10,000 anaesthetized patients, more frequently in special groups and emergency settings (Abdulla, 2013), such as trauma and/or intensive care unit (ICU) patients with altered states of consciousness (e.g., head trauma, alcohol or drug-induced sensoric alterations, cerebrovascular accidents) and/or disabled patients (Aldridge and Taylor, n.d.) and/or elderly patients, and nursing home residents (Mylotte *et al.* 2003a). According to a prospective study that used the level of pepsin in BAL as a surrogate marker of aspiration in ICU patients, 88.9 % of the patients had at least one aspiration episode (Metheny *et al.* 2006).

Unwitnessed gastric aspiration may explain many cases of perioperative pulmonary dysfunction (Marik 2001, Mylotte *et al.* 2003b). The ability to distinguish between the two most common presentations of aspiration syndromes, inflammatory lung injury with aspiration pneumonitis and bacterial aspiration pneumonia, is a challenging task. In addition, the severity of lung injury after aspiration varies according to the amount, composition, and acidity of aspirate, as well as patient-specific features (Son *et al.* 2017).

The severity of a lung injury following gastric aspiration ranges from a mild, subclinical pneumonitis to a progressive respiratory failure with significant morbidity and mortality. Larger aspirated volume can lead to severe complications and a third of patients with aspiration pneumonitis develop a more severe and protracted course that is subsequently linked to ARDS (Raghavendran *et al.* 2011, Warner *et al.* 1993). Patients who present with several risk factors, such as higher age, have an increased risk of aspirating and developing pneumonia or pneumonitis. When other forms of community-acquired pneumonia are compared to aspiration pneumonia, the mortality rate in aspiration pneumonia is substantially higher, with 29.4 % versus 11.6 %, a finding that could imply hospitals that fail to correctly register its presence (Lindenauer *et al.* 2018, Mandell and Niederman 2019). ARDS linked with aspiration pneumonitis has a 30 % mortality rate and is responsible for up to 20 % of all anaesthesia-related

deaths (Nason 2015). Aspiration is also associated with dysphagia, a common and major risk factor that raises mortality rates by 4.69 times in stroke patients (Feng *et al.* 2019).

Clinical presentation, diagnosis and assessment of aspiration syndromes

While macroaspiration is an important feature in aspiration pneumonia and chemical pneumonitis, it is almost impossible to estimate the degree of the exposure because are so uncommon. There is a wide variety of clinical presenting features, from no symptoms to severe discomfort and respiratory failure (Calkovska *et al.* 2019, Mandell and Niederman 2019) which can develop as acute or subacute, and may follow in a progressive or even more progressive manner. Pulmonary aspiration may impact the airway and/or the lung parenchyma. Aspiration pneumonia is usually acute, and symptoms appear fastly, usually within hours or just a few days after the event (Hollaar *et al.* 2016). However, in less aggressive bacteria, anaerobic aspiration can be subacute, and clinical symptoms might be difficult to identify from those of other bacterial pneumonia (Mandell and Niederman 2019). It is important to note that when there is a pulmonary aspiration, patients can also have a chronic cough, asthma attack, or bronchospasm. It is problematic to distinguish between chemical aspiration and other types of aspiration (aspiration pneumonia and aspiration of bland material) because of the event being unwitnessed (Mandell and Niederman 2019). A solid FB may block the airways, resulting in pneumonia and making it difficult to distinguish from bacterial pneumonia. In a study of patients over 65 years of age, it was reported that only around 29 % of patients had large FB obstructions with a delaying diagnosis of between 1 and 3 months while in more than 80 % of the aspiration episodes the foreign object was food (Lin *et al.* 2014).

A considerable proportion of aspirations syndrome cases is caused by noninfectious microaspiration, which is frequently caused by gastric reflux disease. Chronic microaspiration is also considered as a factor in the development of pulmonary fibrosis. Microaspirations of foreign substances, such as chronic lipoid pneumonia, provide the most compelling evidence (DiBardino and Wunderink 2015, Miller *et al.* 2005, Tobin *et al.* 1998).

The diagnosis of aspiration pneumonia depends mainly on the history of disease, medical history, vital

signs and chest radiography. Most often, x-ray investigation reveals a new infiltration in a dependency pulmonary segment. In bed-bound patients, the reverse segments of upper lobes and upper segments of the lower lobes are the dependent pulmonary segments, while lower lobes, especially right, are traditionally affected in ambulatory patients (Bartlett and Gorbach 1975, Marik 2001). Dyspnea with a quick onset, hypoxemia, fever and radiological identification of any bilateral infiltrates or lung auscultation crackles in a hospitalized patient are the most common clinical variables in the diagnosis of aspiration pneumonia (Sanivarapu and Gibson 2021).

Clinical features can help to differentiate aspiration from pneumonitis and pneumonia. In contrast with chemical pneumonitis, the suction event is rarely seen in aspiration pneumonia (Bartlett and Gorbach 1975). Usually, the large amount of gastric content needed for chemical pneumonitis makes it more apparent. Furthermore, hyperacute hypoxemia occurs almost immediately (within hours) as a clinical course of chemical pneumonitis and results in either devastating lung injury or resolution within 48 hours. Patients also have bronchospasm, a frothy sputum, and infiltrates on chest x-ray, including non-dependent areas (Bartlett and Gorbach 1975, Doyle *et al.* 1995, Marik 2001, Mendelson 1946). However, there is no gold standard for distinguishing between these two aspiration events. One option to differentiate aspiration pneumonia and aspiration pneumonitis is to evaluate the level of serum procalcitonin as an appropriate biomarker. Indeed, the serum concentration of procalcitonin increases under various bacterial and viral infections (El-Solh *et al.* 2011, Son *et al.* 2017).

On the chest x-ray, the changes in the right lower lobe are most frequently involved. Patients who have aspirated while upright may have bilateral lower lobe involvement while patients lying in the left lateral decubitus position tend to have left-sided infiltrates. The involvement of the right upper lobe is more common in patients who aspirate in the prone position and those with alcohol use disorder (Sanivarapu and Gibson 2021). Bronchoscopy can identify the aspirated food particles and also enables the retrieval of aspirate sample to be used for microbiological investigation.

Pulmonary aspiration in critically ill patients

Recognition of ARDS is quite low, with slightly more than half of those with mild ARDS and almost 80 % of those with severe ARDS. ARDS is exceedingly

common in critically ill patients and, as a result, it is not well understood or treated (A. Matthay *et al.* 2019). The study involving a multicenter treatment and the evaluation of the outcomes among critically ill patients with aspiration syndromes was conducted (Kane-Gill *et al.* 2007). The risk factors in critically ill patients include impaired consciousness, nasogastric and endotracheal intubation, improper positioning, anesthesia, neurological disorder, alcoholism, the overdose of drugs, and dysfunction of gastrointestinal motility (Kane-Gill *et al.* 2007, Miller *et al.* 2005). The results showed that patients with severe illnesses are more likely to develop aspiration pneumonia, and patients with multilobular aspiration pneumonia have a 90 % mortality rate compared to only one lobe aspiration. Complications related to aspiration infections are not typical, and patients who do not have the symptoms within two hours following the aspiration are not likely to develop further respiratory problems (Kane-Gill *et al.* 2007).

The treatment involved a prescription of antimicrobial therapy for 97 % of the aspiration-suspected patients, and for 100 % of the confirmed pneumonia patients, while 38 % of the patients with suspected suction and 52 % of the patients with aspiration pneumonia were given combination of antibiotics (Huppert *et al.* 2019, Kane-Gill *et al.* 2007). However, antimicrobial therapy for aspiration pneumonia should be carefully considered depending on the aspiration site and type of hospital- or community-acquired pneumonia (Lionel *et al.* 2003). Inappropriate use of antimicrobials includes an increased risk of resistant pathogens being acquired, causing secondary infections, such as vancomycin-resistant Enterococci and *Clostridium difficile*-associated disease, and elevates drug-related costs (Kane-Gill *et al.* 2007, Muto *et al.* 2005). Antimicrobial prescribing is often unnecessarily broad, what raises a concern for the development of bacterial resistance.

Other complication in critically-ill patients is a post-extubation dysphagia (Brodsky *et al.* 2020). Identification of patients at risk of swallowing impairments and implementation of screening tools for dysphagia and aspiration should be the top priority in ICU patients (Brodsky *et al.* 2016, O'Horo *et al.* 2015).

Treatment and management of aspiration syndromes

Prior to attempting to discern between aspiration pneumonitis and pneumonia, it is critical to provide

a prompt care depending on the symptomatology and course of the disease. However, the treatment is distinct for the two aspiration events and consists of supportive management for aspiration pneumonitis and antimicrobial therapy for aspiration pneumonia (Raghavendran *et al.* 2011, Son *et al.* 2017).

Although the data from randomized clinical trials concerning a certain therapy for aspiration are limited, there are some recommended guidelines in the handling of those patients. If an aspiration occurs, the patient should be positioned so that the aspiration for any gastric content is reduced (Raghavendran and Napolitano 2011). The head should be turned laterally to allow a suction from the pharyngeal and oral cavity for patients who are awake. The patient's bed can also be raised with the head upward by a 45-degree angle. Any decision on intubation shall be based on the hypoxia level, neurological status and hemodynamic stability of the patient (Matthay *et al.* 2012, Raghavendran and Napolitano 2011). However, intubation may be required for those patients who have high volume particulate aspiration to facilitate future bronchoscopy (Moore *et al.* 2002). Nebulized bronchodilators may be given in the case of bronchospasm. Mechanical ventilation must continue following the current standards for lung protection strategies. Other interventions to prevent recurring gastric aspiration events, such as placing nasogastric tubes and connecting gastronomic tubes with suction or gravity drainage, should be introduced (Raghavendran and Napolitano 2011).

The role of the bronchoscopy is significant, however, aspirated material is often liquid and disperses rapidly. Hence, routine bronchoscopy with lavage is unlikely to prove useful. Contrary, if the aspirate is predominantly particulate, with clear radiographic evidence of lobar collapse or major atelectasis, a therapeutic bronchoscopy may prove helpful (Raghavendran *et al.* 2011). If a large amount of gastric content is aspirated, bronchoscopy can be used to remove the aspirated gastric fluid and solid material from the central airways, minimizing the inflammatory reaction, preventing atelectasis, and lowering the risk of infection (Marik 2001). In addition, bronchoscopy has the benefit of being able to take a sample of material from the lower part of the respiratory tract. Bacteriological investigation of BAL sample can help to guide a definitive therapy, as well as can allow a discontinuation of antibiotics administration if the cultures do not demonstrate significant bacterial growth (Kollef *et al.* 1995, Matthay

et al. 2012, Raghavendran and Napolitano 2011).

In addition, the role of empirical antibiotics for aspiration management is examined. It was shown that the first-time aspiration occurs as a type of acute pneumonitis, a typical episode of inflammation accompanied by leukocytosis and fever. Although the treatment of aspiration pneumonitis does not require the use of antibiotics, pneumonia can hardly be distinguished (Marik 2001). Although there are no randomized clinical trials in the context of treating ventilator-associated pneumonia (VAP), a short course of antibiotics has not been shown to have adverse effects as long as the antibiotics are de-escalated or discontinued based on quantitative microbiology (Raghavendran *et al.* 2011, Rebuck *et al.* 2001). As a rational strategy in VAP, antibiotics administration may begin and then with the ICU duration it may be reduced. Emphasis is placed on the equal importance of antibiotics elimination, where the culture does not demonstrate a bacterial growth that is significant or that the aspirated material was contaminated (Matthay *et al.* 2012). There should also be considerations to the use of antibiotics in those patients with the aspiration event and simultaneously with the obstruction of the bowel or colonized gastric content (Matthay *et al.* 2019).

The antibiotic therapy is concentrated on the possible pathogens aspirated by a patient, determining that the site was acquired and considering resistant pathogens. However, seriously ill patients get treatment for the risks of dental health and multidrug resistance (Mandell and Niederman 2019). Patients with poor dental health should be considered and clindamycin specifically recommended for patients with pulmonary abscess or lung necrotization should be given (Matthay *et al.* 2019). Application of amoxicillin-clavulanate, moxifloxacin, levofloxacin or clindamycin may be given orally, specifically it is recommended for community-acquired pneumonia (Mandell and Niederman 2019). However, intravenous linezolid or vancomycin administration is recommended in hospitalized patients. Oral administration may be used in some patients with methicillin-resistant *S. aureus* respiratory or nasal colonization (Constantin *et al.* 2019). Routine antibiotic therapy is suggested only when suspected bacterial infection is present and when bronchoscopic cultures are negative, discontinuation is recommended. There is a number of antibiotic therapy management strategies. Medications for antibiotic treatment of aspiration pneumonia are listed in Table 3.

Table 3. Antibiotics (dose, schedule, administration route) used in the treatment of aspiration pneumonia for patients with normal renal function (adjusted according to Mandall and Niederman 2019).

Antibiotic	Dose, Schedule, Administration route
<i>Ampicillin–sulbactam</i>	1.5–3 g every 6 h, intravenous
<i>Amoxicillin–clavulanate</i>	875 mg twice daily, oral
<i>Piperacillin–tazobactam</i>	4.5 g every 8 h or 3.375 g every 6 h, intravenous
<i>Ceftriaxone</i>	1–2 g once daily, intravenous
<i>Cefepime</i>	2 g every 8–12 h, intravenous
<i>Ertapenem</i>	1 g once daily, intravenous
<i>Imipenem</i>	500 mg every 6 h or 1 g every 8 h, intravenous
<i>Meropenem</i>	1 g every 8 h, intravenous
<i>Levofloxacin</i>	750 mg once daily, intravenous or oral
<i>Moxifloxacin</i>	400 mg once daily, intravenous or oral
<i>Clindamycin</i>	450 mg 3/4 times daily, oral; or 600 mg every 8 h, i.v.
<i>Gentamicin or tobramycin</i> †	5–7 mg/kg once daily, intravenous
<i>Amikacin</i> ‡	15 mg/kg once daily, intravenous
<i>Colistin</i> ‡	9 million IU per day in 2/3 divided doses, i.v.
<i>Vancomycin</i> †	15 mg/kg every 12 h, intravenous
<i>Linezolid</i>	600 mg every 12 h, intravenous or oral

† For gentamicin and tobramycin, the dose should be adjusted to a trough level of less than 1 mg per litre, less than 4 mg per litre for amikacin, and 10 to 15 g per millilitre for vancomycin. ‡ The loading dose is 6 million to 9 million IU.

Steroids are not recommended as they show no benefits. Moreover, one study revealed gram-negative pneumonia occurred at a higher rate in patients receiving steroids (Raghavendran *et al.* 2011, Wolfe *et al.* 1977).

Prevention of aspiration pneumonia and pneumonitis

The risk for chemical pneumonitis postoperative procedures can be minimized if patients are required not to eat anything for at least eight hours and not to drink any clear liquids for at least two hours before the surgical procedure (Mandell and Niederman 2019). Preventive effect may also have an avoidance of medications that may disrupt swallowing or that promote aspiration, including antipsychotic agents, sedatives, and antihistamines in high-risk patients (Herzig *et al.* 2017).

Patients who have swallowing disorders, such as those who have had a stroke, should be evaluated for swallowing and talking, oral, rather than enteric tube feeding, and be in the form of mechanical supplementary meals with thickened fluids instead of purified foods and thin liquids (Momosaki 2017). It is recommended that the patients with swallowing difficulty and dysphagia receive nutritional rehabilitation as well as early mobilization to ensure that aspiration pneumonia does not reoccur

(Constantin *et al.* 2019). The patients should receive an enteral feeding in a semirecumbent position to decrease a gastric aspiration risk. Patient with oropharyngeal dysphagia should be positioned with chin down and head turned to one side while feeding and to encourage swallowing of small volumes, multiple swallows, and coughing after each swallow (Macht *et al.* 2014).

There is no certainty about the use of nasogastric tubes for the prevention of aspiration pneumonia. Furthermore, research has indicated that gastric feeding is superior to postpyloric feeding (Mandell and Niederman 2019). Further, a meta-analysis of five randomized controlled trials involving nonventilated patients at risk for pneumonia showed that oral care with chlorhexidine or mechanical oral cleaning was effective in preventing pneumonia. However, chlorhexidine use is controversial and may be associated with increased mortality among ventilated patients, possibly as a result of the toxic effects of chlorhexidine in the lungs (Klompas *et al.* 2014, Mandell and Niederman 2019). The prevention for aspiration pneumonia can be also used for aspiration pneumonitis, but the differences between the two are indicated in terms of prevention because while there are the same steps, additional steps can be used for each.

Conclusion

Aspiration syndromes and associated lung injury represent a complex health problem. Gross aspiration of liquid or particulate matter into lungs can result in severe lung injury and respiratory failure leading to hypoxemia. The initial lung injury is primarily caused by inflammatory mediators rather than bacterial infection. There is no gold standard for distinguishing between the aspiration syndromes. In general, aspiration pneumonitis is witnessed event caused by aspiration of sterile gastric content, whereas aspiration pneumonia is characterized by aspiration of colonized oropharyngeal material. Short summary of the differences in aspiration syndromes can be found in Table 4. The diagnosis should be considered

in the appropriate clinical settings in patients with known risk factors for aspiration and characteristic clinical and radiographic findings. There are various clinical manifestations of microaspiration and macroaspiration, with larger aspiration volume causing more serious repercussions. Aspiration pneumonia is more frequent in hospitalized patients with dysphagia. Initial therapy for acute aspiration depends on a prompt recognition that aspiration has occurred and involves a treatment of acute hypoxemia and bronchospasm (Johnson and Hirsch, 2003). Prophylactic antimicrobial therapy is not effective in patients with acute aspiration pneumonitis, and instead, escalated antibiotic therapy is needed when macroaspiration occurs. Current treatment guidelines for aspiration pneumonia support an initial empirical

Table 4. Aspiration pneumonitis and aspiration pneumonia

	ASPIRATION PNEUMONITIS	ASPIRATION PNEUMONIA
<i>Primary mechanism</i>	Aspiration of sterile gastric contents	Aspiration of colonized oropharyngeal material
<i>Pathophysiology</i>	Acute lung injury	Acute pulmonary inflammatory response
<i>Bacteriology</i>	Initially sterile, potential subsequent bacterial infection	Gram-positive, gram-negative, and rarely anaerobic bacteria
<i>Main risk factors</i>	Depressed level of consciousness	Dysphagia and gastric dysmotility
<i>Age group affected</i>	Regardless of age, usually young people	Usually older people
<i>Aspiration event</i>	Witnessed	Usually not witnessed
<i>Typical demonstration</i>	History of depressed level of consciousness, and pulmonary infiltrate and respiratory symptoms develop	Institutionalized patient with dysphagia; clinical features of pneumonia and an infiltrate in a dependent bronchopulmonary segment develop
<i>Clinical features</i>	No symptoms or symptoms ranging from a non-productive cough to tachypnoea, bronchospasm, bloody or frothy sputum, and respiratory distress 2 or 5 h after aspiration	Tachypnoea, cough, and pneumonia symptoms

antibiotic therapy pending culture results. As demonstrated in this review article, aspiration syndromes with rather high morbidity and mortality are still an important clinical issue. Therefore, the research in this field should continue to further elucidate the pathophysiology, and to improve the screening and treatment of aspiration syndromes.

Conflict of Interest

There is no conflict of interest.

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