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Aspiration pneumonia: A renewed perspective and practical approach

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ABSTRACT

Aspiration pneumonia (AP) is a sub-type of community-acquired pneumonia (CAP) still poorly recognized especially in the absence of an aspiration event. A further difficulty is the differentiation between AP and aspiration pneumonitis. From a clinical perspective, AP is becoming increasingly relevant as a potential cause of severe and life-threatening respiratory infection among frail and very old patients, particularly among those with CAP requiring inpatient care. Moreover, AP is frequently underdiagnosed and a clear-cut definition of this pathological entity is lacking. There are different factors that increase the risk for aspiration, but other common factors influencing oral colonization such as malnutrition, smoking, poor oral hygiene or dry mouth, are also important in the pathogenesis of AP and should be considered. While there is no doubt in the diagnosis of AP in cases of a recent witnessed aspiration of oropharyngeal or gastric content, we here proposed a definition of AP that also includes silent unobserved aspirations. For this reason, the presence of one or more risk factors of oropharyngeal aspiration is required together with one or more risk factors for oral bacterial colonization. This proposed definition based on expert opinion not only unifies the diagnostic criteria of AP, but also provides the possibility to devise easily applicable strategies to prevent oral colonization.

1. Introduction

Pneumonia is a very common acute respiratory infection of the alveoli and distal bronchial tree. Pneumonia is classified into community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP). CAP is defined as pneumonia acquired outside the hospital in subjects who have not been admitted to the hospital in the last month before the onset of symptoms. CAP continues to be the most common cause of death from infectious diseases with an overall incidence rate among adults of 2–5 cases per 1000 person-years [1]. CAP is also associated with significant late mortality up to several years after the initial episode and should be regarded as a major public health threat [2]. The clinical severity of the CAP episode including the need of antimicrobial treatment is a key factor for determining the setting of the patient's care: mild CAP can be managed in the outpatient setting, moderate-to-severe CAP can require treatment in hospital wards, and severe CAP that refers to severely ill patients requires admission to the intensive care unit (ICU).

HAP or nosocomial pneumonia is defined as pneumonia that occurs 48 h or more after hospital admission in a patient without suspicion of incubation on admission. When HAP is acquired in intubated patients after at least 2 days after starting mechanical ventilation treatment, it is called ventilator-associated pneumonia (VAP). VAP accounts for more than 80% of pneumonias acquired in the ICU. Both HAP and VAP are clinically relevant diseases, not only because of high morbidity and mortality, particularly in patients with infections caused by multi-resistant pathogens, but also for the impact in the quality of life and economic burden.

The reason to divide pneumonia in CAP and HAP is because of differences in the majority of causative pathogens. In CAP, *Streptococcus pneumoniae*, viruses, *Haemophilus influenzae*, atypical bacteria, and *Legionella* spp. are the causative microorganisms (in different frequencies as described in the next section). On the other hand in HAP (and VAP) the most frequent microorganisms are *Staphylococcus aureus* both methicillin-sensitive and methicillin-resistant, *Enterobacteriaceae* spp., non-fermenting Gram negative bacilli (*Pseudomonas aeruginosa*) and *Acinetobacter* spp.

The differences in the microbiology are mainly due to different risk

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factors of the hosts including gastric and oropharyngeal colonization. In addition and as it is described in another section, the etiopathogenesis of CAP is different from that of HAP. On the other hand, the etiopathogenesis of VAP is also different from HAP since it occurs in patients with an endotracheal tube in place. Also, both CAP and HAP can occur in non-immunosuppressed and immunosuppressed patients, and again the microorganisms differ. However, most of the information reported in the literature corresponds to immunocompetent patients. However, CAP and HAP in immunosuppressed patients have been recently a focus of increasing interest.

Aspiration pneumonia is a CAP, the definition, clinical presentation and diagnosis of which remain challenging to clinicians. It is expected to have an increasing contribution in mortality and morbidity, particularly in the elderly population over the next coming decades. Among patients hospitalized for CAP, an aspiration event causes pneumonia in 5% of patients less than 80 years of age and in 10% of patients aged 80 years or older [3]. In nursing home resident pneumonias, an amount from 18% to 30% is related to an aspiration event [4]. In frail patients, the prevalence of aspiration pneumonia is 10 times higher [5]. Viruses, however, do not play a role in aspiration pneumonia.

Despite progress in identifying risk factors and understanding of the microbiology of aspiration pneumonia, a clear definition of the disease is lacking. This article aims to present a contextualized definition of aspiration pneumonia based on recent advances in the understanding of risk factors, particularly those related to oral colonization, as well as advances in diagnostic strategies, microbiological etiology and the role of lung microbiome in the pathogenesis of the disease. Under a renewed perspective and practical approach, the definition of aspiration pneumonia here proposed is intended to clarify differences between aspiration pneumonitis and aspiration pneumonia and to be broadly used by researchers and clinicians, allowing to collect more precise epidemiological data and target antimicrobial therapy more effectively.

2. Aspiration pneumonia and aspiration pneumonitis

Aspiration refers to the inhalation of gross oropharyngeal or gastric contents into the larynx and lower respiratory tract [6]. Several pulmonary syndromes may occur after aspiration, depending on the amount and nature of the aspirated material, the frequency of aspiration and the host's response to the aspirated material [6]. Aspiration pneumonia is an infectious process of proliferation and invasion of pulmonary parenchyma caused by the inhalation of oropharyngeal secretions that are colonized by pathogenic bacteria, whereas aspiration pneumonitis is a chemical injury caused by the inhalation of sterile gastric contents.

The development of lung infection depends largely on host defense mechanisms [7] and the virulence of the aspirated pathogen and, to a less extent, on the inoculum size [8,9]. Large volumes of gastric aspirates are sufficient to produce chemical pneumonitis or pneumonia but not all aspiration events lead to pneumonia [10]. It is important to differentiate infection from pneumonitis due to the parenchymal inflammatory reaction induced by hydrochloric acid content of gastric secretions [6]. If the pH of gastric content is neutralized before aspiration, the pulmonary injury would be minimal and it may resolve without antibiotic therapy, but it can reduce host defenses increasing the risk of later infection [11].

Aspiration pneumonitis is historically associated to a disturbance of consciousness such as that resulting from a drug overdose, seizures, or the use of anesthesia (Mendelson's syndrome), but in some patients the episode of aspiration is not witnessed. However, the major aspiration pneumonitis is frequently misdiagnosed and treated with antibiotics caused by failure to distinguish from pneumonia aspiration and the tendency to consider all pulmonary complications of aspiration to be infectious. Unfortunately, the usefulness of biomarkers in evaluating these pulmonary syndromes is understudied and cannot be of help to guide the differential diagnosis between aspiration pneumonia and pneumonitis [12].

On the other hand, when the healthy adults aspirate small amounts of oropharyngeal secretions during sleep [13], the low burden of virulent bacteria in normal pharyngeal secretions together with powerful passive coughing active ciliary clearance, and resident alveolar macrophages can clear the inoculum without sequelae. But if these mechanisms are impaired or if the amount of aspirated material is sufficiently large, pneumonia may follow [6]. Due to these considerations, we believe that new diagnostic criteria of aspiration pneumonia would allow us to detect cases of aspiration pneumonitis and optimize our use of antibiotics.

2.1. *Risk factors for aspiration*

In the majority of patients in whom there is a suspicion of aspiration pneumonia, history of an apparent or overt aspiration is lacking. In these cases, the presence of silent aspiration should be considered as well as other risk factors for aspiration. Silent aspiration following stroke has been reported in 40–70% of patients [6]. In residential care facilities, the prevalence of silent aspiration is 59%–70% [5]. In a case-control study of community-acquired pneumonia in the elderly, the videofluoroscopic study demonstrated penetration into the laryngeal vestibule or aspiration during swallow in 52.8% of cases [14].

There are many risk factors for aspiration, although there is confusion about the extent to which these factors actually contribute to aspiration pneumonia. Advanced age is a well-established risk factor for oropharyngeal dysphagia. In a case-control study of elderly patients aged $\geq$70 years hospitalized with pneumonia, the prevalence of oropharyngeal dysphagia was 91.7%, with silent aspiration in half of them [14]. However, the concept of frailty defined as a clinically recognizable state of older adults with increased vulnerability is more adequate than older people based on chronological age [15]. Gastroesophageal disorders, including esophageal motility disorders, gastrostomy, and gastroesophageal reflux disease can cause aspiration pneumonia. Impaired deglution safety and aspirations have been also reported in neurological disorders, stroke and altered mental status, including decreased consciousness in cases of alcoholism, seizures or drug overdose. The use of sedatives, hypnotics, or psychotropic drugs reduces the swallowing reflex and favor muscle relaxation [16]. Likewise, patients with symptoms of obstructive sleep apnea are at risk of increased pharyngeal aspiration as well as special circumstances, including enteral nutrition, endotracheal intubation, upper gastrointestinal endoscopy, bronchoscopy, after event of cardiac arrest, etc.

However, if only aspiration (silent or evident) is considered for diagnosis of aspiration pneumonia, the diagnosis may be overestimated and more false positives will be obtained at the time of defining aspiration pneumonia in the setting of patients with one or more risk factors for increased oropharyngeal aspiration. Therefore, the presence of respiratory pathogens in the aspirated material is a relevant factor. In this respect, the existence of risk factors for colonization of the oropharyngeal cavity should be included in the definition of aspiration pneumonia. A high prevalence of colonization of the nasopharyngeal and oropharyngeal cavity by respiratory pathogens in older people has been reported [17], although prevalence rates vary according to age, living with children, or place of acquisition of infection (community, nosocomial, nursing home).

A poor nutritional status is another risk factor, which has been shown to be closely associated with oropharyngeal dysphagia and to impact negatively on the immune system [18]. Tobacco smoking is a well-known risk factor for pneumonia with a positive trend increasing in the duration of the habit, the average number of cigarettes smoked daily, and cumulative cigarette consumption. Five years after smoking' cessation, former smokers had a 50% reduction in the risk of pneumonia. Tobacco smoking modifies buccal epithelial surfaces which causes increased pneumococcal adherence and may lead to greater oropharyngeal colonization and hence a greater risk of developing CAP. In a population-based case-control study of 1336 incident cases of

community-acquired pneumonia, poor oral health was a risk factor for infection [19]. Oral hygiene practices are particularly important in subjects with dental dysesthesia and dental prosthesis. In a systematic review of observational studies, poor oral health was a definitive and modifiable risk factor for pneumonia [20]. In hospitalized patients with poor nutrition, poor oral hygiene was associated with a high odds ratio for the presence of pneumonia-causing bacteria [21].

In addition, other risk factors for pneumonia reported in different studies include a recent history of inappropriate antibiotic treatment, dry mouth due to poor water ingestion or poor salivary production, and a number of special situations that can affect oropharyngeal colonization, such as tracheal cannulation, medications use that can modify gastric pH (proton-pump inhibitors, histamine H2 blockers) enteral nutrition and use of inhalers.

The presence of one or more of these risk factors in the appropriate clinical setting may suggest a diagnosis of aspiration pneumonia [22].

2.2. Pathogenesis and microbiology

Culture independent molecular techniques have shown that the lower respiratory tract, historically considered sterile in healthy subjects, contains diverse communities of microbes: the lung microbiome [23]. Different communities of bacteria are present both in health and in disease states, and the study of the lung microbiome has provided new insights in the pathogenesis of lung infection, including aspiration pneumonia. The lung bacterial microbiome shares greater community membership with communities of the oropharynx, and this similarity suggests that the upper respiratory tract is the primary source of microbial immigration to the lungs, via microaspiration during daytime and aspiration during sleep [24]. Dysphagia is also involved but the effect of aspirated volume and frequency of aspirations on microbiome is unclear. However, dysbiosis and disequilibrium of oropharyngeal bacterial communities contributes to decreased colonization resistance and reduced containment of potential pathogens, leading to dissemination and subsequent development of pneumonia.

The causative organisms of aspiration pneumonia depend on those residing in the oral cavity. *S. pneumoniae*, *H. influenzae*, and *S. aureus* are common pathogens in CAP. In older nursing home residents as well as in patients with HAP, *S. aureus* is the main causative pathogen followed by Gram-negative bacilli (e.g. *Klebsiella pneumoniae* and *Escherichia coli*) as well as *P. aeruginosa* and *S. pneumonia* [25].

The microbiological etiology of aspiration pneumonia may depend from different aspects. In the CAP, age, smoking habit, alcohol abuse and comorbidities (chronic obstructive pulmonary disease-COPD, diabetes mellitus, liver disease, renal failure, and neurological illness) influence the type of pathogen occurring [26,27].

Few studies concern the etiology of aspiration pneumonia. In hospitalized elderly patients with severe aspiration pneumonia, the most of bacteria are gram negative (*E. coli*, *K. pneumoniae*, *Serratia* spp., *Proteus* spp.) followed by *S. aureus* and *S. pneumoniae* [28]. Anaerobic bacteria are infrequent causative pathogens of aspiration pneumonia and it has been recently shown that hospitalized patients with aspiration CAP or CAP with aspiration risk factors had similar anaerobic flora compared to patients without aspiration risk factors [29].

2.3. Diagnostic algorithm

Besides assessment of clinical features of pneumonia [20–33], confirmation of radiological signs of pneumonia in a characteristic bronchopulmonary segment on chest radiography [25] or high-resolution computed tomography in selected cases is indispensable for the diagnosis. Lung ultrasound has also a high sensitivity and specific for the diagnosis of pneumonia [34]. However, a chest radiograph may be negative early in the course of aspiration pneumonia because the radiographic changes generally develop 24 h after aspiration [35]. If the patient is elderly and frail, or if the clinical suspicion is uncertain, then the next test should probably be a lung ultrasound. Only the small number of patients who have an uncertain diagnosis after both a chest radiograph and ultrasound will then need a CT scan. However, locations of radiological features depend on the position of the patient before the aspiration event as they are different if the patient is lying in a supine, semi-recumbent, or upright position because of the effect of gravity. In supine positions, the posterior segments of the right upper lobe and the right apical segment of the lower lobe are the areas most likely affected. In the standing and sitting positions, the basal segments of the lower lobes, particularly of the right lower lobe, are usually affected.

The diagnosis of aspiration pneumonia is highly probable in a patient with suggestive clinical symptoms, radiographic evidence of pulmonary infiltrate in a commonly involved lung site when aspiration occurs, and in the presence of a previous direct observation of aspiration. However, even in these clear circumstances, the presence of more than one oral contamination risk factors should be considered to exclude the diagnosis of aspiration pneumonitis.

Taken into consideration the different factors involved in the pathogenesis of aspiration pneumonia, a diagnostic algorithm to distinguish between aspiration pneumonia and aspiration pneumonitis is proposed (Fig. 1). This algorithm that combines clinical and radiological signs of pneumonia, observation of aspiration, and the presence of risk factors for both aspiration and oral colonization, is readily applicable in clinical practice.

Although a discussion of the treatment strategies is not the objective of this review, treatment depends on the place of acquisition of pneumonia, the severity of clinical picture and the possibility of resistant pathogens as the cause of the disease. It seems necessary to use effective antibiotics against anaerobic microorganisms unless there is poor dental health. Initial treatment with antibiotics is not indicated in the presence of a diagnosis of chemical pneumonitis. On the other hand, preventive strategies in relation to modifiable risk factors can be recommended, both in relation to oropharynx colonization (avoidance of medications that modify gastric pH (proton pump inhibitors, histamine H2 blockers, inhalers) and dysphagia (thickening agents, functional rehabilitation). Finally, when the diagnosis of aspiration pneumonia has been establish, it is important to assess the presence of silent aspiration using a clinical and/or imaging test to exclude dysphagia.

3. Concluding remarks

AP is a clinically relevant respiratory infection, which is becoming increasingly frequent among special populations including frail and elderly patients as well as among those with CAP requiring inpatient care. The diagnosis of AP can be easily establish when there is evidence of overt aspiration events, but in cases of silent unobserved aspirations, diagnosis of AP can be challenging. Different well known risk factors for gastric or oropharyngeal aspiration as well as for oral bacterial colonization should be considered for unifying a definition of AP, which also would provide the possibility to establish preventive strategy measures. The diagnostic algorithm here proposed based on expert opinion combining the presence of one or more risk factors for aspiration and oral bacterial colonization allows differentiation of AP from bacterial pneumonitis and is easily applicable in daily practice.

Declaration of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Declaration of competing interest

The four authors have contributed to the study according to international consensus on authorship of the ICMJE and have seen and approved the final draft. No funding was received for this clinical review

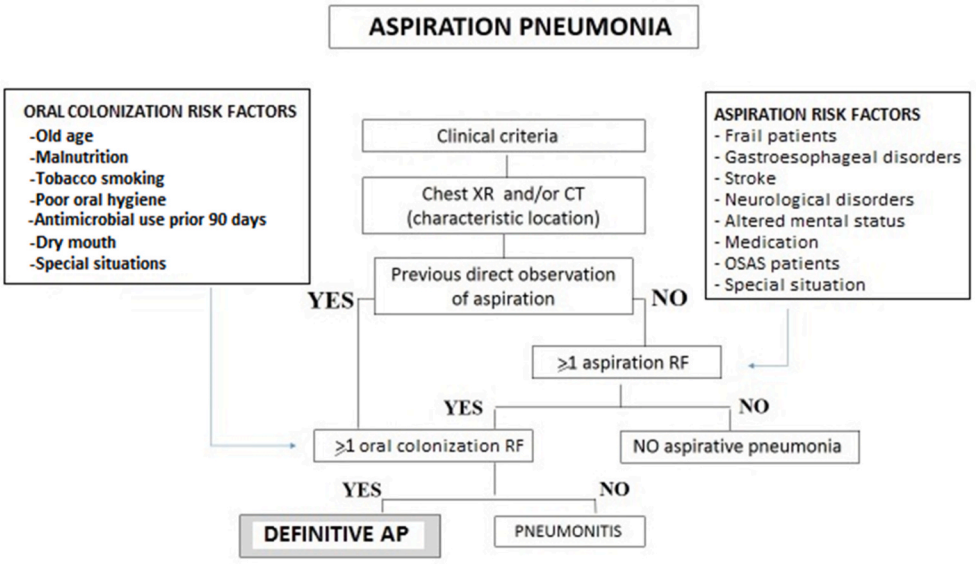

Fig. 1. Algorithm for the diagnosis of aspiration pneumonia and aspiration pneumonitis. Clinical criteria for a diagnosis of pneumonia are the presence of acute respiratory symptoms with fever (or without fever in older people) associated with newly identified and modified infiltrates in characteristic location on chest radiography. Special situations in oral colonization risk factors include tracheal cannulation, medications that modify gastric pH (proton pump inhibitors, histamine H2 blockers), enteral nutrition, and use of inhalers. Special situation in aspiration risk factors include enteral nutrition, endotracheal intubation, upper gastrointestinal endoscopy, and after an event of cardiac arrest (XR: X-rays, CT: computed tomography, OSAS: obstructive sleep apnea syndrome, RF: risk factor).

and none of the authors has any conflict of interest to be disclosed.

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