CRITICAL REVIEW

The Triple Threat of Aspiration Pneumonia*

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Aspiration pneumonia is a disease recognized since antiquity, yet there are few conditions in pulmonary medicine as frequent in occurrence but as lacking in consensus regarding classification and treatment. The priority for clinical description belongs to Hippocrates, the first scientific investigation is ascribed to John Hunter in 1781, and the “classic study” is credited to Mendelson in 1946. Despite the plethora of reports in recent years, many physicians are confused by the variables in clinical descriptions and therapeutic recommendations.

A major theme in the large collected case reports is that pulmonary complications of aspiration seldom occur in otherwise healthy persons. Thus, aspiration pneumonia is usually associated with an underlying disease. To define the clinical conditions associated with aspiration pneumonia, two sources of data can be employed. The first are reports of the incidence of this complication among all patients with specific diseases. For example, aspiration pneumonia has been incriminated as a leading cause of fatalities associated with anesthesia, head injuries, cerebrovascular accidents and debilitating diseases. Recurrent or chronic aspiration pneumonitis has been noted in 10-20 percent of patients with gastroesophageal reflux or achalasia.

Another approach to understanding the clinical setting is to study all patients diagnosed as having aspiration pneumonia. In these reports, the principal underlying conditions are alcoholism, seizure disorders, cerebrovascular accidents, drug addiction, general anesthesia, esophageal disease and nasogastric tube feeding.

These studies have defined the population at risk for developing aspiration pneumonia. Predisposing conditions are reduced levels of consciousness with consequent compromise of glottic closure and cough reflexes; dysphagia from neurologic or esophageal disorders; and mechanical disruption of the “cardiac sphincter” due to nasogastric feeding tubes. The common denominator is a breakdown of normal protective mechanisms with subsequent entry of gastric secretions, oropharyngeal secretions or exogenous food or fluids into the bronchial passages.

At the same time it must be recognized that aspiration into the lungs is common and is usually well tolerated. Several investigators have instilled dye into the stomach preoperatively, and then analyzed for the dye in the tracheobronchial tree during the operative procedure. The marker was detected in the tracheal aspirate in 7-16 percent of patients undergoing surgery, although pulmonary complications were seldom observed. In a similar experiment, Cameron et al demonstrated aspiration of dye placed on the tongue in 69 percent of tracheostomized patients. This could not be correlated with progressive pulmonary disease. Additionally, Amberson noted that contrast material dropped into the mouths of sleeping patients was detected in the lung on x-ray films the following morning. Again, there were no ill-effects. These studies suggest that aspiration of gastric contents and oropharyngeal secretions is common, generally passing unrecognized with no sequelae. The decisive factor among patients who develop pulmonary complications is presumably related to the frequency, volume and character of the aspirate.

There is an unfortunate tendency to combine the pulmonary complications of aspiration under a single banner, ie “aspiration pneumonia.” In fact, there are three distinct aspiration syndromes which are best categorized according to the nature of the inoculum (Table 1). This classification determines the pathophysiologic mechanisms and dictates the therapeutic approach.
Table 1—Classification of Aspiration Syndromes According to the Inoculum

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
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<tbody>
<tr>
<td>Toxic fluids - chemical pneumonitis</td>
<td>Acid, Hydrocarbons, Alcohol, Bile, Mineral oil, Animal fats</td>
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<tr>
<td>Bacterial pathogens - bacterial infection</td>
<td>Fungi, Bacteria, Viruses</td>
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<tr>
<td>Inert substances - airway obstruction</td>
<td>Fluids, Particulate matter</td>
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Aspiration of Toxic Fluids

Certain fluids are toxic to the lower respiratory tract and can initiate an inflammatory reaction which is independent of bacterial infection. Examples include acids, animal fats, mineral oil, alcohol and hydrocarbons. Of these, gastric acid is the most frequently encountered and the most completely studied.

The toxic effect of acid on the lung was originally reported by Winternitz et al in an experimental animal study of irritant war gases during World War I. They described the syndrome in animals, which was subsequently documented by Mendelson in a clinical study of 66 obstetrical patients who aspirated gastric contents during anesthesia. Mendelson found two types of pulmonary sequellae. Five patients aspirated food particles and had acute obstructive reactions. The remaining 61 aspirated liquid gastric contents, and developed what has come to be known as “Mendelson’s syndrome.” Initially, there was an abrupt onset of acute respiratory distress. Bronchospasm was a characteristic feature in all patients, leading him to conclude that “this type of reaction may be likened to an acute asthmatic attack.” Uniformly, these patients had chest x-ray film changes consisting of soft, irregular, mottled densities in the right lower lobe or both lower lobes. Although the patients were considered critically ill, their clinical course stabilized after one to two days and they generally had uneventful recoveries. In fact, there were only two deaths in this series and both occurred among the five patients who aspirated solid particles. It is of interest that infection was regarded as an infrequent secondary complication. Twenty patients were febrile and eight eventually developed bacterial pulmonary infection; antimicrobials (sulfonamides or penicillin) were administered to 19 of the 66 patients.

Clinical Presentation: Since the original description, there have been multiple reports of “Mendelson’s syndrome” in nonobstetrical patients. The outstanding clinical features are antecedent observed aspiration, precipitous onset of acute dyspnea (usually within two hours when aspiration has been observed), bronchospasm, chest x-ray films showing mottled densities in the lower lobes, and frothy, nonpurulent sputum. Many patients are hypotensive due to an immediate reflex reaction or to subsequent intravascular volume depletion with fluid aggregation in the lung. The most characteristic physiologic feature is hypoxia, with arterial PO2 determinations often in the range of 35-50 mm Hg, in association with a normal or low PCO2, indicating ventilation-perfusion disturbances. Pulmonary function tests indicate reduced compliance related to edema, hemorrhage and microatelectasis. These patients can

Figure 1. Serial chest x-ray films taken at two to three hour intervals after suspected aspiration of gastric acid. The patient was admitted with an incarcerated inguinal hernia and protracted vomiting. At approximately 2:30 PM aspiration was observed followed by immediate dyspnea and wheezing. Blood gas determinations at 3:00 PM revealed PO2—41, PCO2—28 and pH—7.3. The initial chest x-ray film at 3:30 PM (a) showed right lower lobe pneumonitis. Subsequent x-ray films at 5:30 PM (b) and 8:30 PM (c) showed progressive infiltrates involving both lower lobes. A transtracheal aspirate that night revealed no bacteria on gram stain or culture.
progress to the adult respiratory distress syndrome with stiff lungs and physiologic shunting. A representative case of acid pneumonitis is summarized in Figure 1.

In contrast to Mendelson's earlier experience, the mortality rates in more recent studies are an imposing 30-70 percent. It is uncertain whether the increased lethality represents a more severe form of the disease, the occurrence in more compromised hosts than obstetrical patients, or the inclusion in several reports of patients who actually had airway obstruction rather than chemical pneumonitis.

Pathophysiology: Mendelson's syndrome involves the toxic effect of gastric acid on the lung and has been equated with a chemical burn. The entire sequence of events has been reproduced by the intratracheal inoculation of sterile hydrochloric acid in experimental animals. Saline, saliva and neutralized gastric acid, on the other hand, produce only transient respiratory distress with no x-ray film changes. Both the pH and the volume of the inoculum appear to be crucial factors in reproducing the disease. Using graded doses of hydrochloric acid, there is no toxic reaction with a pH above 2.4. The extent of pathology is inversely related to the pH below this level. Additionally, the experimental studies have generally employed an acid inoculum of 1-4 ml/kg. Translated to the human this represents rather large volume, ie 50-300 ml, and this may account for the fact that the aspiratory event is actually observed in many clinical reports of Mendelson's syndrome.

Experimental animal studies have shown that toxic effects of acid are immediate and extensive. Hamelburg and Bosomworth infused sterile filtered gastric juice with methylene blue in an isolated perfused lung. The dye marker was detected at the lung surface after just 12-18 seconds and there was extensive atelectasis within three minutes. Post-mortem studies in both experimental animals and patients with acid pneumonitis reveal peribronchial hemorrhage and exudate, pulmonary edema and areas of necrosis.

Treatment: The most important facet of treating Mendelson's syndrome is to correct hypoxia by vigorous and immediate assisted ventilation or positive pressure oxygen. Repeated tracheal suction is often necessary to maintain a clear airway. Intravenous fluid support is also important, particularly when there is hypotension. X-ray film changes and frothy sputum may suggest pulmonary edema due to congestive failure, but the patient actually has intravascular volume depletion and the central venous pressure is low. Although the data are conflicting, most experimental and clinical studies support the efficacy of short-term corticosteroid therapy if initiated within 12-24 hours of acid aspiration. Suggested daily doses range from 600 mg-1600 mg hydrocortisone to as much as 1-2 gm methylprednisolone for two to four days. Intratracheal inoculation of buffering solutions is ill-advised since aspirated acid is neutralized within minutes by the tracheobronchial secretions. Similarly, pulmonary lavage is futile since the full extent of injury has usually occurred by the time the diagnosis is recognized. Local installations of diluents are specifically contraindicated, for this would add mechanical obstruction to an already compromised airway.

The role of antimicrobials in acid pneumonitis is controversial. Most authorities conclude that bacteria play no role in the initial acute events. This impression is supported by experimental animal data which show no difference whether the inoculum of gastric contents is fresh or boiled (to remove bacteria). Clinical studies, however, have shown that bacterial infection may follow in the wake of aspiration of gastric contents. Furthermore, recent animal studies indicate that the lung injured by acid is particularly susceptible to a bacterial challenge. If antibiotics are used, it is necessary to appreciate that their role is secondary to the more compelling and immediate considerations of aggressive respiratory support, tracheal suction, intravenous fluids and corticosteroids. Antimicrobials may be given initially on the premise that infection is likely and prophylaxis with its attendant risks is justified. It is our view that antibiotics should be reserved for cases in which there is evolving evidence of infection such as significant fever, purulent sputum, leukocytosis and progressive infiltrates. There is little evidence that early use of antibiotics actually prevents subsequent infection, but it is clear that these drugs will select a more resistant bacterial flora. Whether antibiotics are used for prophylaxis or actual therapy, the selection of agents should take into account that these events usually occur within a hospital, and likely pathogens include aerobic gram-negative bacilli as well as the usual oropharyngeal bacteria.

Aspiration of Pathogenic Bacteria

The most common form of aspiration pneumonia bears the hallmarks of bacterial pulmonary infection from the start, namely fever and purulent sputum. This condition is a less fulminant process than acid pneumonitis, and the actual episode of aspiration is seldom observed. The diagnosis, however, is suspect when typical symptoms occur in a susceptible host who has roentgenographic changes in a dependent

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pulmonary segment.

Presentation: The course of bacterial infections following aspiration was documented in the pre-antibiotic era when the natural history of this disease could be followed without intervening chemotherapy.43-46 The initial lesion was pneumonitis, and the symptoms in the early stages were often mild. After 8-14 days there was a tendency to observe tissue necrosis with abscess formation or extension to the pleural space. It is noteworthy that purulent discharge and cavitation on chest x-ray examination were not present until this later stage of disease.

The presenting findings depend largely on the point in this sequence of events at which the patient is observed. Patients seen early in their course will have roentgenographic evidence of pneumonitis which may resemble other forms of bacterial pneumonia, but the distinctive features are the more insidious onset and an underlying illness which predisposes to aspiration. Favored anatomic sites of involvement are those subject to gravitational flow; the posterior segments of upper lobes or superior segments of lower lobes which are dependent in the recumbent position, and the basal segments of the lower lobes which are dependent in the upright position.47 Patients who are observed later in the course of the process, ie one to two weeks after aspiration, are likely to have cavitation or empyema formation.

Bacteriology: The aspirated inculum is composed largely of oropharyngeal secretions, especially saliva containing bacteria pooled from the tongue, gingiva, buccal mucosa and pharynx. Gastric contents may also be aspirated and the bacteria from this source are similar to those of the upper respiratory passages.48 Quantitative cultures of saliva yield approximately 10^8 bacteria/ml with anaerobes outnumbering aerobic and facultative bacteria by a factor of 5-10 to 1.48 The number of anaerobes is likely to be even greater in patients with poor oral hygiene; gingivitis exudate, for example, contains concentrations of anaerobes of 10^11/ml, a figure which approaches the numerical limits of bacteria which can occupy this given mass.49 In terms of specific bacteria the flora is extremely complex. Rosebury lists 21 different genera of bacteria which are considered normal cohabitants of the upper respiratory tract passages. Organisms which assume the greatest importance in terms of pathogenic potential are anaerobic streptococci, Fusobacteria and Bacteroides melaninogenicus. Among patients who are hospitalized there is likely to be oropharyngeal colonization with enteric gram-negative bacilli (E coli, Klebsiella, etc.), Pseudomonas or

Staph aureus.50 These organisms must be considered potential pulmonary pathogens in aspiration pneumonia acquired within a hospital.

The bacteriology of infections following aspiration in 70 human subjects has been recently studied in our laboratory (Table 2).51 All patients in our series had a condition predisposing to aspiration and roentgenographic evidence of infection in a dependent pulmonary segment. To establish the bacterial etiology of the pulmonary infection, we relied entirely upon specimens collected before antimicrobial treatment and devoid of oropharyngeal contamination, ie transtracheal aspirates, empyema fluid and blood cultures. The infecting flora was often complex, and there was an average of 2.9 different bacterial species in each case. Anaerobic bacteria were recovered from 61 patients (87 percent), and were the exclusive isolates in 32 (46 percent). The predominant anaerobic organisms were anaerobic gram-positive cocci, Bacteroides melaninogenicus and Fusobacterium nucleatum. As anticipated, there were important differences in the bacteriology of patients who aspirated during hospitalization. Among 32 patients in this category there was a higher isolation rate of aerobic pathogens, particularly gram-negative bacilli and Staph aureus. These findings have recently been confirmed by Lorber and Swenson.17

Experimental studies: The experimental counterpart of this form of aspiration pneumonia was described in the 1930's by David Smith52,53 who noted that bacteria seen in histologic section of lung abscess walls were identical to those recovered in gingivitis exudate. He reproduced the disease by

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<td>Community Acquired</td>
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<tr>
<td>Cases</td>
</tr>
<tr>
<td>Anaerobes only</td>
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<tr>
<td>Aerobes only</td>
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<tr>
<td>Anaerobes plus aerobes</td>
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<tr>
<td>Major anaerobic isolates</td>
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<tr>
<td><em>Bacteroides melaninogenicus</em></td>
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<tr>
<td><em>B fragilis</em></td>
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<td><em>B oralis</em></td>
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<tr>
<td><em>Fusobacterium nucleatum</em></td>
</tr>
<tr>
<td>Peptostreptococci</td>
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<tr>
<td>Peptococci</td>
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<tr>
<td>Major aerobic isolates</td>
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<tr>
<td><em>Diplococcus pneumoniae</em></td>
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<tr>
<td><em>Staph aureus</em></td>
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<tr>
<td>Klebsiella</td>
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<tr>
<td><em>Pseudomonas aeruginosa</em></td>
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<tr>
<td><em>Escherichia coli</em></td>
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<td><em>Enterobacter cloacaee</em></td>
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inoculating 0.25-0.5 ml of pyorrhea pus into the trachea of experimental animals. If insufficient anesthesia was used, the animals coughed up the inoculum and had no pulmonary complications. With more prolonged anesthesia, however, a typical sequence of events ensued. Initially, there was pneumonia which was followed after 8-14 days by the appearance of putrid pulmonary abscesses. Smith extracted four anaerobic species which appeared to dominate in the abscess cavities—fusobacteria, streptococci, vibrios and spirochetes. (More complete identification is not available since anaerobic taxonomy at that time was generally restricted to oxygen-sensitivity testing and stain morphology.) Smith used recombined cultures of these organisms and showed that all four bacterial types were necessary to reproduce the disease. These studies suggest that no single organism could be considered pathogenic by itself, but that several bacteria acted in concert to cause the infection.

**Treatment:** Antimicrobial therapy of pulmonary infections following aspiration is optimally based on cultivation of a reliable specimen source. Expectorated sputum is unsuitable since these specimens are invariably contaminated by oropharyngeal bacteria during passage through the upper airways. Gram stain of vigorously washed sputum proved useful in the prechemotherapeutic era, but this procedure seldom has been performed in more recent years. Moreover, the morphologic features of the many likely pathogens are not sufficiently distinctive to permit firm conclusions. The implication is that unless there is bacteremia or empyema, a transtracheal aspiration is required to establish a bacteriologic diagnosis. This approach is often unrealistic, for many physicians are not familiar with this procedure, and there are rare but serious complications. Fortunately, the bacteriology of these infections is generally predictable on the basis of the previous studies so that familiarity with these results provides initial guidelines for chemotherapy.

The major pathogens in community-acquired cases of aspiration pneumonia are the anaerobic bacteria indicated above, and these strains are susceptible to penicillin G. The major exception is *Bacteroides fragilis* which has been recovered in 15-20 percent of patients. Our preliminary studies suggest that pulmonary infections involving this organism will respond satisfactorily to penicillin G despite *in vitro* resistance. Thus, this antibiotic is considered the drug of choice for aspiration pneumonia acquired outside the hospital. Cases acquired during hospitalization are likely to involve facultative gram-negative bacilli or *Staph aureus*, as well as anaerobic bacteria. Empirical selection of antibiotics in this setting should include a combination of agents to provide activity against both the aerobic and anaerobic components of the infection. Our choice is gentamicin in combination with a semisynthetic penicillin (oxacillin or nafcillin), clindamycin or a cephalosporin (cephalothin or cefazolin).

**Aspiration of Inert Substances**

Patients may aspirate material which has no toxic effect on the lung but causes pulmonary complications by mechanical obstruction or by a reflex mechanism.

**Fluids:** Fluids which produce no distinctive pulmonary lesions include saline solution, water, barium, and neutralized gastric contents. Intratracheal inoculation of limited quantities of these substances to anesthetized animals generally causes only transient respiratory distress. Certain animal studies using precise physiologic measurements have demonstrated hypoxia and reduced compliance which can be reversed with isoproterenol. These effects appear to represent an intrinsic pulmonary reflex reaction which is independent of the chemical composition of the inoculum. On the basis of these studies, therapy for this condition involves intermittent positive pressure breathing with 100 percent oxygen combined with isoproterenol.

Aspiration of large volumes of nontoxic fluids produces abrupt suffocation by mechanical obstruction. Failure to clear the airways may be impaired in patients who lack an effective cough reflex due to a neurologic deficit or coma. The obvious therapeutic modality is immediate tracheal suction. In the absence of a residual pulmonary infiltrate, no further treatment is indicated.

**Solid particles:** Aspiration of particulate material causes variable degrees of respiratory obstruction. Most cases occur in children of one to three years and the usual objects involved, in order of prevalence, are peanuts, other vegetal particles, inorganic material and teeth.

Initial symptoms following aspiration of particulate material depend on the relative size of the object and the caliber of the tracheobronchial tree. Large objects lodge in the larynx or trachea causing sudden respiratory distress, apnea, cyanosis and death. The term “cafe coronary” has been aptly applied to note that this event may simulate an acute myocardial infarction and it has a peculiar propensity to occur in restaurants.

Smaller objects reach peripheral airways causing complete or partial obstruction. The initial symptom is cough due to bronchial irritation. When major bronchi are involved there may be severe dyspnea, cyanosis, wheezing, chest pain, nausea and vomiting.
Chest x-ray films in this early stage show atelectasis or obstructive emphysema. Expiration films are particularly helpful in detecting the latter lesion.\textsuperscript{61} Bacterial infection often follows if particulate material in the lower respiratory tract is not removed within one to two weeks.\textsuperscript{62,64} Types of infectious complications include pneumonitis (often recurrent), bronchiectasis, lung abscess and empyema. Thus, there are two distinctive periods in which these patients are likely to seek medical attention—the early obstructive or irritative phase and a later stage characterized by bacterial complications.

The experimental counterpart of this sequence has been studied by Lansing et al.\textsuperscript{65} These investigators occluded bronchi in dogs with sterile cotton swabs inserted through a bronchoscope. Initially there was acute atelectasis, but all symptoms subsided if the obstructing lesion was eliminated within 24-72 hours. Examination of the extracted plugs showed that a mucopurulent exudate collected on the distal side. Cultures of this material yielded a mixture of aerobic and anaerobic bacteria apparently derived from the oropharyngeal flora.

The obvious therapeutic recommendation for retained particulate material in the lower respiratory tract is extraction, usually with bronchoscopy. Infections complications generally respond to penicillin providing the underlying lesion is eliminated.

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