Treatment of anaerobic pulmonary infections

Aspiration pneumonia and lung abscess typically involve a polymicrobial flora derived from the gingival crevice of a host who is prone to aspirate owing to compromised consciousness or dysphagia. The predominant pathogens in most patients are anaerobic bacteria. Guidelines for antibiotic management during the post-penicillin era may be divided into two periods. The first period was from the late 1940s until the early 1970s when the bacteriology of these infections was poorly understood, but penicillin was widely accepted as the preferred antimicrobial agent for both aspiration pneumonia and lung abscess. In the early 1970s, there were multiple publications dealing with the pathophysiology and bacteriology of lung abscess and aspiration pneumonia. Paradoxically, the improved understanding of these infections was accompanied by considerable confusion and debate regarding antibiotic selection.

The natural history of anaerobic pulmonary infections begins with aspiration of relatively large numbers of anaerobic bacteria from the upper airways, primarily the gingival crevice (Bartlett, 1987). The host characteristically has an underlying condition, causing compromised consciousness or dysphagia. Examples include alcoholism, drug addiction, neurological disorders, convulsions, general anaesthesia, oesophageal disease, intubation and so forth.

The initial infection is pneumonitis with X-ray evidence of a pulmonary infiltrate, which usually appears in a dependent pulmonary segment. The most frequent locations are the superior segment of a lower lobe or the posterior segment of an upper lobe, which sites are dependent in the recumbent position, or the lower lobes, which are dependent in the upright position. Symptoms during the early phase of infection may resemble those noted with other bacterial infections of the lung, but the process is usually more subtle and many patients do not present for medical care until after several weeks when supplicative complications have occurred. Patients seen in the early pneumonitis stage usually lack the two findings that represent the major clues to anaerobic infection: purulent sputum and tissue necrosis with lung abscess or empyema. Thus, the presentation is often pneumonitis in a patient with expectorated sputum cultures showing no likely pathogen, a combination now commonly referred to as 'enigmatic pneumonia'. The usual drug advocated in this setting is erythromycin, in view of its activity against Mycoplasma pneumoniae, Chlamydia pneumoniae (TWAR agent) and Legionella species as well as Streptococcus pneumoniae. The frequency with which anaerobes account for 'enigmatic pneumonia' is not known. The problem is that the invasive diagnostic techniques necessary to verify anaerobic bacteria in the lower airways are rarely used. Nevertheless, prospective studies of pneumonia in unselected patients studied by transtracheal aspiration or fiberoptic bronchoscopy using a brush catheter indicate that anaerobic bacteria may account for as many as 20–30% of unselected patients with pneumonia (Ries, Levison & Kaye, 1974; Pollack et al., 1983).

Another common source of misunderstanding concerns the appellation 'aspiration pneumonia' since this actually applies to at least three different syndromes involving abnormal entry of exogenous or endogenous fluids or particulate matter into the lower
The bacterial aetiology of anaerobic pulmonary infections is rarely established in the present era. In the early 1970s there were multiple studies utilizing transtracheal aspiration as a method to obtain uncontaminated specimens from the lower airways that would be valid for anaerobic culture. These studies showed that anaerobic bacteria were present in 60–80% of patients with aspiration pneumonia or lung abscess (Bartlett & Finegold, 1974; Lorber & Swenson, 1974; Gonzalez-C. & Calie, 1975; Brook & Finegold, 1980). Patients with community-acquired aspiration pneumonitis usually had specimens that yielded only anaerobic bacteria or anaerobes in combination with penicillin-sensitive aerobic bacteria. By contrast, aspiration pneumonia acquired in the hospital reflected the bacteriology of nosocomial infections with anaerobic bacteria commonly found in association with aerobic Gram-negative bacilli or staphylococci (Lorber & Swenson, 1974; Bartlett et al., 1986; Bartlett, 1987).

With regard to specific anaerobic bacteria, the 'big three' were anaerobic streptococci (Peptostreptococcus species), Bacteroides melaninogenicus and Fusobacterium nucleatum. These studies in the early 1970s also showed that B. fragilis, notable as a penicillin-resistant organism, was recovered in 15–20% of cases. The high yield of B. fragilis was difficult to understand since this organism is not known to colonize the upper airways, the presumed source of bacteria in both aspiration pneumonia and lung abscess. This apparent paradox has now been clarified with more recent studies indicating that organisms previously identified as B. fragilis were probably erroneously classified (Finegold, George & Mulligan, 1985). Nevertheless, this more recent work does indicate that 20–25% of patients with lung abscess or aspiration pneumonia harbour anaerobic bacteria that are resistant to penicillin, most often by the mechanism of penicillinase production.

The diagnostic studies necessary to verify the presence of anaerobic bacteria in the lower airways requires uncontaminated specimens such as empyema fluid, transthoracic aspiration or transtracheal aspiration (Beerens & Tahon-Castel, 1965; Bartlett, Rosenblatt & Finegold, 1973). Alternatively, specialized techniques such as fibreoptic bronchoscopy with the protected brush and quantitative cultures, may be acceptable if rigorous standards are established (Wimberly et al., 1982; Pollack et al., 1983). None of these techniques are considered reliable for the recovery of anaerobic bacteria after the initiation of antibiotic treatment (Bartlett, 1977; Wimberly et al., 1982). The great majority of patients never undergo these procedures. One of the reasons is that transtracheal aspiration, the technique most frequently used 15–20 years ago, has become almost extinct, so that there are now relatively few physicians skilled in the procedure. The result is that nearly all patients with anaerobic pulmonary infections are treated with antibiotics selected empirically.

The empirical selection of antimicrobial agents seemed to be far simpler in the 1950s and 1960s when the bacteriology was ill-defined and penicillin was widely accepted as the drug of choice. Perhaps the most extensive studies of lung abscess were by William Weiss and his colleagues at Philadelphia General Hospital who reported a series of studies involving approximately 76 patients (Weiss, 1968, 1970, 1973). This investigator demonstrated that about 95% of patients responded to penicillin, that the occasional penicillin failure responded to substitution of tetracycline, and that high dose oral phenoxymethylpenicillin V (750 mg four times daily) was as successful as intravenous penicillin. Penicillin also became the preferred agent for aspiration pneumonia on the basis of similar studies.
The studies in the early 1970s that defined the bacteriology of anaerobic pulmonary infections necessitated reconsideration of antibiotic options. As noted, 20–25% of patients had anaerobic bacteria that were resistant to penicillin. These included not only B. fragilis, but also B. ruminicola, B. gracilis, B. wadsworthensis and the black-pigmenting Bacteroides species (formerly B. melaninogenicus) (Finegold et al., 1985). Much of the initial concern was based on these microbiological observations. A counter argument to changing antibiotic recommendations was the nagging feeling that these are polymicrobial infections and no one has demonstrated the need to treat all components of such mixed infections. Furthermore, the arguments were largely theoretical since clinical failures with penicillin seemed to be unusual. The debate concerning preferred drugs for aspiration pneumonia and lung abscesses continued until 1983 when Levison et al. (1983) reported the only large prospective study comparing antibiotic regimens in anaerobic lung infections in recent times. This study compared intravenous penicillin (10 million units per day) with clindamycin given intravenously initially and then orally. The results of this study showed a statistically significant benefit for clindamycin over penicillin in terms of the number of patients who responded, the time to resolution of fever and the time to resolution of putrid sputum. This trial also included randomization to treatment for three weeks or six weeks in an attempt to define the optimal duration of treatment, but this question was never answered.

Another drug that has attracted considerable attention for anaerobic infections in the last decade is metronidazole (Eykyn, 1983). However, the collected experience of 28 patients with putrid lung abscess in three series showed that metronidazole as a single agent failed in 12 (43%) (Tally, Sutter & Finegold, 1979; Sanders, Hanna & Lewis, 1979; Petline, 1981). The probable explanation for this inadequate performance is the poor activity of metronidazole against the aerobic and microaerophilic streptococci that are especially common in these infections. Thus, metronidazole should not be used unless combined with another drug such as penicillin.

The result of the above observations is that three antimicrobial regimens are now commonly advocated for anaerobic infections, as follows.

1. Aqueous benzylpenicillin given intravenously. Some authorities still consider this to be the 'gold standard' despite inferiority in the comparative trial with clindamycin.
2. Clindamycin 600 mg intravenously every 8 h. Many authorities consider this to be the preferred agent on the basis of both in-vitro sensitivity tests and clinical experience.
3. Penicillin combined with metronidazole, each given intravenously or orally. This regimen has excellent in-vitro activity against clinical isolates, but relatively few published studies to verify its clinical effectiveness.

Most patients with lung abscess receive parenteral therapy which should continue until they have become afebrile and show clinical improvement. Subsequent therapy may be by the oral route for an arbitrary duration. We generally continue oral therapy until serially collected X-rays show complete resolution or a small stable residual scar. This often requires several weeks or even months of treatment, especially with large abscess cavities. It should be noted that the need for parenteral therapy for lung abscesses is not well established; outpatient therapy may be associated with peripheral neuropathies. The major disadvantage of penicillins is failure to respond, with extended morbidity and prolonged hospitalization.

It is likely that a multitude of antibiotics would actually prove effective in treating anaerobic pulmonary infections, but the clinical experience with alternative agents is meagre. Virtually all penicillins except the anti-staphylococcal agents are as effective as benzylpenicillin in vitro and could be substituted in penicillin-containing regimens. Probably preferred for oral use are amoxycillin or phenoxymethylpenicillin, because of their improved absorption. Agents that combine a β-lactam and a β-lactamase inhibitor are extremely active against the microbes involved in these cases and suffer only from the lack of an extensive published experience. The same applies to imipenem, chloramphenicol and cefoxitin. Most cephalosporins, with the exception of cefoxitin and latamoxef, are less active than penicillins in vitro, but I expect that...
many would work reasonably well if there was another reason to use them. Perhaps the best justification would be a mixed infection in which these drugs would be required for the aerobic component.

Similar guidelines presumably apply to aspiration pneumonia involving anaerobic bacteria as well. It is conceivable that patients with pneumonitis respond better than patients who already have tissue necrosis with abscess formation. In a retrospective analysis of 46 patients with anaerobic pneumonitis verified by transtracheal aspiration, we noted that the rate of response and time for defervescence following penicillin therapy was identical to that noted in 46 patients with pneumococcal pneumonia (Bartlett, 1987). Unfortunately, there are relatively few therapeutic trials to provide scientific data for antibiotic selection in patients with aspiration pneumonitis so we are stuck with the observations on lung abscess. An important question raised earlier concerns the utility of erythromycin since patients with aspiration pneumonia may be commonly treated under the guise of 'enigmatic pneumonia'. Erythromycin shows good activity against most anaerobic bacteria involved in anaerobic pulmonary infections with the exception of fusobacteria, but fusobacteria are among the 'big three'. Tetracycline was once a favoured drug for these infections, particularly in patients who failed to respond to penicillin. In-vitro activity against the organisms commonly isolated is often marginal and few authorities now recommend use in this setting.

A final comment concerns procedures directed at facilitating drainage in patients with lung abscess. Methods commonly advocated include bronchoscopy and physical therapy — less commonly, surgery or percutaneous drainage. The logic of emphasizing the importance of drainage is our heritage from the surgical adage that 'pus must be drained'. The problem with application of this principle to lung abscess is that virtually all cases drain themselves via the bronchi, which happening usually accounts for the air-fluid level seen on chest X-ray. The potential impact of bronchoscopy as therapy was well studied in the pre-chemotherapeutic era, before and after introduction of the Jackson bronchoscope. Summaries of the literature at that time showed the mortality rate was 34% without antibiotics and bronchoscopy had no impact (Allen & Blackman, 1936; Smith & Durham, 1948). Although bronchoscopy was at one time routinely advocated in virtually all patients with lung abscess, this procedure is now generally used only as a diagnostic manoeuvre in patients with an atypical presentation, suspected neoplasm or failure to respond (Sosenko & Glassroth, 1983). Aggressive drainage may not only be useless, it may be harmful. The author is aware of three patients who had airway obstruction and death following drainage of lung abscesses into the contralateral lung. The point to emphasize is that antibiotics represent the mainstay of therapy for lung abscess, and that facilitation of drainage, by bronchoscopy or physical therapy, should be done with due caution.

The results of medical management of lung abscess, once a controversial, territorial issue between thoracic surgery and medicine, have been extremely rewarding. The mortality rate of 30–35% for untreated infections has been reduced to 5–10% and most of the patients who do poorly are those with severe associated conditions (Pohlson et al., 1985; Bartlett, 1987). Nevertheless, there are still occasional patients who prove refractory to treatment. Poor prognostic findings include large cavity size, prolonged symptoms prior to presentation, abscess associated with bronchial obstruction and serious associated conditions, such as old age, debility or neoplasm. Approximately 10% of patients with lung abscess are considered candidates for surgical drainage procedures, most commonly because of failure of medical management. The usual procedure is lobectomy or, occasionally, pneumonectomy. Some patients have rapid progression of symptoms with a perceived need for urgent drainage, but also have prohibitive operative risks. A suggested approach in such cases is percutaneous drainage with appropriate care to avoid contamination of pleural space (Weissberg, 1984; Snow, Lucas & Horrigan, 1985).

JOHN G. BARTLETT
Division of Infectious Disease,
The Johns Hopkins Hospital,
Baltimore,
Maryland 21205, USA

References
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