Paul Marik

Aliens, anaerobes, and the lung!

P. Marik (✉)
Department of Critical Care,
University of Pittsburgh, Medical School,
640A Scaife Hall, 3550 Terrace Street, Pittsburgh, PA, 15261, USA
e-mail: maripe@ccm.upmc.edu
Tel.: +1-412-6475387, Fax: +1-412-6478060

The period from 1965 to 1980 has been referred to as the "anaerobic renaissance" [1]. This was facilitated by the development of a good taxonomic order for anaerobes, the development of the GasPak jar that made it possible for laboratories to cultivate oxygen-sensitive forms, and several clinical studies demonstrating a high yield of anaerobes [1]. However, the anaerobic renaissance is now over. Thirty years ago anaerobes accounted for 20–30% of isolates from blood cultures [2]. Currently less than 3% of blood cultures yield an anaerobe, with only about 0.4% representing true anaerobic bacteremia [3, 4]. While anaerobes remain important pathogens in polymicrobial abdominal sepsis [5, 6], their pathogenetic role outside the abdomen appears less clear.

Anaerobic bacteria have low intrinsic virulence. While the cell wall of some anaerobes such as *Fusobacterium* and *Bacteroides* contain lipopolysaccharide, they lack the lipid A component of conventional endotoxin and therefore do not cause the sepsis syndrome associated with Gram-negative bacteria [7]. Putative virulence factors include the bacterial capsule, toxin formation, and production of enzymes such as superoxide dismutase, collegenase, and proteases. However, the pathogenicity of anaerobes is largely explained by bacterial synergy [8]. While individually these organisms are of low virulence, synergy between facultative organisms and anaerobic bacteria are required to cause infection and abscess formation. This was elegantly demonstrated by a set of experiments performed by David Smith [9] in 1926. This investigator cultured pieces of membrane from patients with Vincent's angina. Each of the organisms isolated in pure culture was then injected separately into the groin and lungs of mice and guinea pigs. None of the organisms alone produced disease; a mixture of at least four bacteria was required to produce an abscess. This study performed almost 80 years ago is supported by more recent clinical studies. Single anaerobic organisms have rarely been reported to cause clinical infection; most studies report multiple anaerobic species together with aerobic or facultative organisms [5, 6, 10, 11, 12]. Each component of a mixed infection with aerobes and anaerobes may help perpetuate the infection. The lowering of the oxidative-reduction potential of the microenvironment by facultative organisms creates more favorable conditions for the growth of anaerobes, whereas anaerobes themselves promote the survival of facultative organisms through their antiphagocytic properties.

Anaerobes may play an important role in a limited number of extra-abdominal infections, including necrotizing soft tissue infections, empyema, lung abscess, and brain abscess [10, 11, 12, 13]. However, these are now uncommon infections in Westernized nations. Furthermore, while previous studies indicated anaerobes to be the predominant pathogen in patients with chronic sinusitis and chronic otitis media, recent data suggest that these organisms are present in fewer than 10% of infections [14].

What about the role of anaerobic bacteria in patients with pneumonia? On the basis that most forms of pneumonia are caused by the aspiration of oropharyngeal material, and that anaerobes are found in high concentration in the gingival crypts it has been assumed that anaerobes play an important pathogenetic role in patients with community-acquired, nosocomial, and ventilator-associated pneumonia. Indeed, many physicians treat patients with

these conditions using antibiotics that have anaerobic activity. However, the data supporting this practice are lacking. Some argue that the failure to grow anaerobes is because of inadequate culture techniques or the use of antibiotics which kill these highly sensitive organisms, stating, "I know they are there, I just can't prove it." However, this argument carries as much scientific weight as the belief in alien visitations to earth. Many believe in alien abductions and visitations but cannot provide any credible evidence to support their contention.

The current compulsion to treat pneumonia with anaerobic antibiotics can be traced to four clinical studies performed in the early 1970s which investigated the role of anaerobic bacteria in patients with "aspiration pneumonia" [15, 16, 17, 18]. All four studies demonstrated anaerobes in more than 90% of patients. Based on these four studies millions of patients have been treated with antibiotics having anaerobic activity. It should be pointed out, however, that the patients included in these studies are not representative of those seen today in Western countries; many of these patients had been symptomatic for up to 140 days, were coughing voluminous amounts of purulent material, and were diagnosed with lung abscesses. In addition, these studies are plagued by a major methodological flaw, namely that the samples for microbial culture were obtained by transtracheal aspiration. Only one study, to my knowledge, has been published that investigated the accuracy of transtracheal aspiration in the diagnosis of pneumonia [19]. Moser and colleagues [19] demonstrated contamination with upper respiratory flora in 30% of dogs undergoing transtracheal aspiration. Furthermore, transtracheal aspirates had a very low diagnostic sensitivity and specificity in animals with pneumonia. More recent studies which have sought to determine the microbiological cause of community-acquired, nosocomial, and ventilator-associated pneumonia have found anaerobes to constitute fewer than 2% of isolates [20, 21, 22, 23]. Furthermore, most of these anaerobes were mono-microbial isolates, suggesting that these organisms represent oropharyngeal contamination with anaerobes rather than true infection. Indeed, pure anaerobic commu-

nity-acquired pneumonia is so uncommon that such a diagnosis is worthy of publication as a case report [24]. The only recent study which has implicated anaerobes as important pathogens in ventilator-associated pneumonia is that by Dore and colleagues [25]. These authors isolated anaerobic bacteria in 23% of patients with a first episode of ventilator associated pneumonia.

In *Intensive Care Medicine* Robert and colleagues [26] present an additional study in which they investigated colonization of the lower respiratory tract with anaerobic bacteria in mechanically ventilated patients. Using protected lower respiratory tract sampling these authors identified 28 anaerobic organisms in 22 of 26 mechanically ventilated patients. Five patients subsequently developed ventilator-associated pneumonia, with isolation of anaerobic bacteria in two cases. Five anaerobes and one aerobe (*Streptococcus viridans*) were isolated from these two patients. Considering that *S. viridans* is usually not considered a pulmonary pathogen but rather a contaminant and the requirement for multiple anaerobic and facultative aerobes to cause infection, it is not clear from the data presented that the anaerobes isolated represent real pulmonary pathogens.

Determining the pathogenetic role (if any) of anaerobes in pneumonia is not merely an interesting academic exercise. Antibiotics with anaerobic activity have a profound effect on the endogenous bacterial flora which play an important role in colonization resistance. The use of antimicrobial agents with anaerobic activity is associated with colonization and infection with vancomycin-resistant enterococci and *Clostridium difficile* [27, 28]. These are both potentially fatal infections in hospitalized patients. I submit that significantly more patients have died as consequence of these infections following the use of antianaerobic agents to treat pneumonia than would have died from untreated anaerobic lung infections. The use of these drugs must be restricted. Indeed, hospital-wide policies that restrict the use of clindamycin have been demonstrated to reduce the incidence of *C. difficile* associated diarrhea and vancomycin-resistant enterococci colonization [29, 30].

References

1. Bartlett JG, Dick J (2000) The controversy regarding routine anaerobic blood cultures. Am J Med 108:505–506
2. Wilson W, Martin W, Washington J (1972) Anaerobic bacteraemia. Mayo Clin Proc 47:649
3. Ortiz E, Sande MA (2000) Routine use of anaerobic blood cultures: are they still indicated? Am J Med 108:445–447
4. James PA, al Shafi KM (2000) Clinical value of anaerobic blood culture: a retrospective analysis of positive patient episodes. J Clin Pathol 53:231–233
5. Brook I, Frazier EH (2000) Aerobic and anaerobic microbiology in intra-abdominal infections associated with diverticulitis. J Med Microbiol 49:827–830
6. Brook I (1989) A 12 year study of aerobic and anaerobic bacteria in intra-abdominal and postsurgical abdominal wound infections. Surg Gynecol Obstet 169:387–392
7. Styrt B, Gorbach SL (1989) Recent developments in the understanding of the pathogenesis and treatment of anaerobic infections. I. N Engl J Med 321:298–302
8. Bartlett JG (1990) Anaerobic bacteria: general concepts. In: Mandell GL, Douglas RG, Bennett JE (eds) Principles and practice of infectious diseases, 3rd edn. Churchill Livingstone, New York, pp 1828–1842

9. Smith DT (1930) Fusospirochetal disease of the lungs produced with cultures from Vincent's angina. J Infect Dis 46:303–310

10. Elliott D, Kufera JA, Myers RA (2000) The microbiology of necrotizing soft tissue infections. Am J Surg 179:361–366

11. Hammond JM, Potgieter PD, Hanslo D, Scott H, Roditi D (1995) The etiology and antimicrobial susceptibility patterns of microorganisms in acute community-acquired lung abscess. Chest 108:937–941

12. Brook I, Frazier EH (1993) Aerobic and anaerobic microbiology of empyema. A retrospective review in two military hospitals. Chest 103:1502–1507

13. Chaudhry R, Dhawan B, Laxmi BV, Mehta VS (1998) The microbial spectrum of brain abscess with special reference to anaerobic bacteria. Br J Neurosurg 12:127–130

14. Ramdan HH (1995) The role of anaerobes in chronic sinusitis. Arch Otolaryngol Head Neck Surg 121:591

15. Bartlett JG, Gorbach SL, Feinegold SM (1974) The bacteriology of aspiration pneumonia. Am J Med 56:202–217

16. Lorber B, Swenson RM (1974) Bacteriology of aspiration pneumonia: a prospective study of community- and hospital-acquired cases. Ann Intern Med 81:329–331

17. Gonzalez CCL, Calia FM (1975) Bacteriologic flora of aspiration-induced pulmonary infections. Arch Intern Med 135:711–714

18. Bartlett JG, Gorbach SL (1975) Treatment of aspiration pneumonia and primary lung abscess. Penicillin G vs clindamycin. JAMA 234:935–937

19. Moser KM, Mauer J, Jasey L, Kremsdorf R, Konopka R, Shure D, Harrell JH (1982) Sensitivity, specificity, and risk of diagnostic procedures in a canine model of *Streptococcus pneumoniae* pneumonia. Am Rev Respir Dis 125:436–442

20. Combes A, Figliolini C, Trouillet JL, Kassis N, Wolff M, Gibert C, Chastre J (2002) Incidence and outcome of poly-microbial ventilator-associated pneumonia. Chest 121:1618–1623

21. Chastre J, Fagon JY (2002) Ventilator-associated pneumonia. Am J Respir Crit Care Med 165:867–903

22. Saito A, Hara K, Yamaguchi K, Usui T (1984) Pulmonary infection due to anaerobes in a hospital autopsy survey. Rev Infect Dis 6 [Suppl 1]: S128–S131

23. Marik PE, Careau P (1999) The role of anaerobes in patients with ventilator-associated pneumonia and aspiration pneumonia. A prospective study. Chest 115:178–183

24. Swartz MA, Marino PL (1990) Anaerobic bacterial pneumonia in an otherwise healthy young adult. Postgrad Med 77:87–88

25. Dore P, Robert R, Grollier G, Rouffineau J, Lanquetot H, Charriere JM, Fauchere JL (1996) Incidence of anaerobes in ventilator-associated pneumonia with use of a protected specimen brush. Am J Respir Crit Care Med 153:1292–1298

26. Robert R, Grollier G, Frat JP, Godet C, Adoun M, Fauchere JL, Dore P (2003) Colonization of the lower respiratory tract with anaerobic bacteria in mechanically ventilated patients. Intensive Care Med (http://dx.doi.org/10.1007/s00134-003-1729-8)

27. Donskey CJ, Chowdhry TK, Hecker MT, Hoyen CK, Hanrahan JA, Hujer AM, Hutton-Thomas RA, Whalen CC, Bonomo RA, Rice LB (2000) Effect of antibiotic therapy on the density of vancomycin-resistant enterococci in the stool of colonized patients. N Engl J Med 343:1925–1932

28. Johnson S, Samore MH, Farrow KA, Killgore GE, Tenover FC, Lyras D, Rood JI, DeGirolami P, Baltch AL, Rafferty ME, Pear SM, Gerding DN (1999) Epidemics of diarrhea caused by a clindamycin-resistant strain of Clostridium difficile in four hospitals. N Engl J Med 341:1645–1651

29. Climo MW, Israel DS, Wong ES, Williams D, Coudron P, Markowitz SM (1998) Hospital-wide restriction of clindamycin: effect on the incidence of Clostridium difficile-associated diarrhea and cost. Ann Intern Med 128:989–995

30. Quale J, Landman D, Saurina G, Atwood E, DiTore V, Patel K (1996) Manipulation of a hospital anti-microbial formulary to control an outbreak of vancomycin-resistant enterococci. Clin Infect Dis 23:1020–1025