Review

Clinical review: Bacteremia caused by anaerobic bacteria in children

Itzhak Brook

Department of Pediatrics, Georgetown University School of Medicine, Washington DC, USA

Correspondence: Itzhak Brook, ib6@georgetown.edu

Published online: 9 May 2002 *Critical Care* 2002, **6**:205-211

Abstract

This review describes the microbiology, diagnosis and management of bacteremia caused by anaerobic bacteria in children. *Bacteroides fragilis*, *Peptostreptococcus* sp., *Clostridium* sp., and *Fusobacterium* sp. were the most common clinically significant anaerobic isolates. The strains of anaerobic organisms found depended, to a large extent, on the portal of entry and the underlying disease. Predisposing conditions include: malignant neoplasms, immunodeficiencies, chronic renal insufficiency, decubitus ulcers, perforation of viscus and appendicitis, and neonatal age. Organisms identical to those causing anaerobic bacteremia can often be recovered from other infected sites that may have served as a source of persistent bacteremia. When anaerobes resistant to penicillin are suspected or isolated, antimicrobial drugs such as clindamycin, chloramphenicol, metronidazole, cefoxitin, a carbapenem, or the combination of a beta-lactamase inhibitor and a penicillin should be administered. The early recognition of anaerobic bacteremia and administration of appropriate antimicrobial and surgical therapy play a significant role in preventing mortality and morbidity in pediatric patients.

Keywords anaerobic bacteria, bacteremia, children, *Bacteroides fragilis*, *Peptostreptoccus* sp., *Clostridium* sp.

Infections caused by anaerobic bacteria can occur in children, and may be serious and life-threatening. The recent increased recovery of these organisms from children has led to greater appreciation of the role anaerobes play in pediatric infections at all body sites, including the bacteremia.

Anaerobes are one of the predominant components of the normal human skin flora and the most predominant component of the bacterial flora of the mucous membranes [1], and are therefore a common cause of bacterial infections of endogenous origin. Because of their fastidious nature, these organisms are difficult to isolate from infectious sites, and are often overlooked. Their exact frequency is difficult to ascertain because of the inconsistent use of adequate methods for their isolation and identification. A lack of direct adequate therapy against these organisms may lead to clinical failures. Their isolation requires appropriate methods of collection, transportation and cultivation of specimens [1]. Treatment of anaerobic infection is complicated by the slow growth of these organisms, by their polymicrobial nature and by the growing resistance of anaerobic bacteria to antimicrobial drugs.

Although anaerobes have been reported to account for 8% to 11% of episodes of bacteremia in adults [1], anaerobic organisms have rarely been isolated from blood cultures of pediatric patients. These microbes represent a small percentage of the total number of positive blood cultures recovered from children, which may be because of the difficulty in isolating and identifying these organisms. There is, however, a growing awareness of the role of anaerobes in bacteremia [2–7], especially in children with certain predisposing conditions and in newborns, who are at high risk, and in those with necrotizing enterocolitis. This review describes the microbiology and management of bacteremia due to anaerobic bacteria in children.

Incidence

In a survey of anaerobic infections in children, blood cultures have been found to be the second most frequent source of anaerobic organisms [2–4]. In one of these reviews of the recovery of anaerobes from children in a university hospital over a period of one year [5], 13 blood cultures were positive and contained 14 anaerobes. In a large prospective study

lasting a year, only 0.3% of blood cultures contained anaerobic bacteria that were involved in the pathogenesis of the patient's disease [4]. In contrast, pathogenic aerobes were recovered from 9% of the cultures tested during that period. Anaerobes accounted for 5.8% of all bacteremic episodes (8.7% in the newborn period and 4.8% in children over 1 year of age). Notably, 10% of the newborns with clinical bacteremia had only anaerobes recovered from their blood cultures.

Zaidi *et al*. [8], reviewed the use of anaerobic blood cultures for children and noted that 15 (2.1%) of 723 cases of bacteremia were caused by strict anaerobes and they concluded that use of the entire volume of blood drawn should be reserved for aerobic cultures. Recent studies have suggested that there has been a decline in the incidence of anaerobic bacteremia. Some authors [9–13] have speculated that this might be as a result of the use of bowel preparations prior to abdominal surgery and the more routine use of antibiotics active against anaerobes.

Microbiology

Anaerobic bacteremia has rarely been described in pediatric patients [13,14]. Sanders and Stevenson [7] in a review of the literature in 1968 summarized 11 cases of *Bacteroides* bacteremias in children. In one study, anaerobic organisms were recovered from 6 of 34 children who required general anesthesia and nasotracheal intubation for dental repair [15]. Another study documented bacteremia in 28 children who were undergoing dental manipulations [16]. Among the 28 isolates recovered, 21 were anaerobes (*Propionibacterium* sp., nine; *Veillonella alcalescens*, five; *Prevotella melaninogenica*, three; *Peptostreptococcus* sp., two; and *Eubacterium* sp. and *Fusobacterium* sp., one each).

Brook *et al*. [5] reviewed their experience in recovery of anaerobes in the blood over a 12-month period. A total of 13 blood cultures were positive and contained 14 anaerobic agents: five were *Bacteroides fragilis*, three others were *Bacteroides* sp., two were *Fusobacterium* sp., three were *Propionibacterium* sp., and one was *Peptostreptococcus* sp. In one instance two organisms were isolated from a blood culture: *Peptostreptococcus* sp. and *Fusobacterium* sp.

Dunkle *et al*. [3] recovered 14 anaerobes from blood cultures over a 1-year study. The dominant anaerobes recovered were *Clostridium* sp. (four), *Fusobacterium nucleatus* (three species), Gram-positive cocci (three species), and *B. fragilis* (two species). Although 27 isolates of *Propionibacterium acnes* were recovered, only three were associated with clinical infection.

Thirmuoothi *et al*. [4] reviewed their experience over a period of 18 months, and reported 35 anaerobic isolates from 34 blood cultures. The predominant isolates were four each of Gram-positive cocci and *Bacteroides* sp. and two isolates each of *Fusobacterium* sp., *Bifidobacterium* sp., and *Clostridium* sp. Although *Propionibacterium* sp. were recovered in 18 instances, there was no apparent relationship between their recovery from the blood and the 18 patients' clinical illness.

Brook and colleagues [17] summarized their experience in the diagnosis of anaerobic bacteremia noted in 28 children. Twenty-nine anaerobic isolates were recovered from 28 patients ranging in age from 1 week to 15 years. Of these isolates, 14 were *Bacteroides* sp. (11 of which belonged to the *B. fragilis* group); four were *Clostridium* sp.; four were anaerobic Gram-positive cocci; four were *P. acnes*; and three were *Fusobacterium* sp. Although the predominant isolate from blood cultures (56–65%) is *P. acnes* [2,3], a normal inhabitant of the skin, many of these isolates may reflect contamination of the blood cultures by the skin flora. *Propionibacterium acnes* can cause bacteremia, however, especially in association with shunt infections [18]. All of the patients with *P. acnes* bacteremia included in the study by Brook *et al*. [17] had clinical infection, and all but one responded to antimicrobial therapy. Furthermore, two patients had meningitis caused by this organism after installation of cardiovascular shunts.

An important aspect of anaerobic bacteremia is that anaerobes frequently are present in cases of polymicrobial bacteremia [1], reflecting the fact that localized anaerobic infections are usually polymicrobial. Polymicrobial bacteremia involving anaerobic bacteria were reported by several authors. Frommell and Todd [19] reported 56 children with bacteremia with multiple bacterial isolates. Five anaerobes were isolated: two *Bacteroides* sp., two *Peptostreptococci* and one *Clostridium perfringens*. Rosenfeld and Jameson [20] reported a 15-year-old child with polymicrobial bacteremia involving seven isolates (including four *Bacteroides* sp. and an anaerobic cocci) associated with pharyngotonsillitis. Seidenfeld *et al*. [21] reported an adolescent with a fatal bacteremia caused by *Fusobacterium necrophorum* and *Peptostreptococcus* sp. associated with peritonsillar abscess. Givner *et al*. [22] recovered *Bacteroides capillosus* with *Corynebacterium hemolyticum* from the blood of a child with primary Epstein–Barr virus infection who developed sinusitis.

Caya and Truant summarized 65 cases of non-infant pediatric clostridial bacteremia [23]. The predominant isolates were *Clostridium septicum* (25 isolates), *Clostridium perfringens* (21 isolates) and *Clostridium tertium* (six isolates). Of the 63 children analyzed, 29 (46%) survived their episode of clostridial bacteremia. Three clinical indices were shown to have a statistically significant negative impact on survival: hypotension, hemolysis and lack of antibiotic therapy. Of the 36 patients with known underlying neoplastic disease, 27 had acute leukemia, five had sarcoma, three had a malignant lymphoproliferative disorder and one had glioblastoma multiforme. Of the 23 patients with no underlying neoplasia, three of them had cyclic neutropenia, two were in sickle cell disease crisis, two had neutropenia associated with aplastic

anemia, and one was mildly immunocompromised as a result of renal transplantation.

Brook reported the microbiology of 101 specimens obtained from 95 children with malignancy [24]. A total of 17 patients had bacteremia. Four had *Escherichia coli*, in one instance mixed with *B. fragilis*. *Bacteroides fragilis* group isolates were recovered in three instances (two in patients with leukemia who had a perirectal abscess), *Staphylococcus aureus* in three patients, *Clostridium* spp. in two (one *C. perfringens* and one *C. septicum*) and two *Proteus* spp.

Brook summarized clinical and microbiological data of 296 adults with anaerobic bacteremia [25]. Anaerobes were isolated with aerobic or facultative bacteremia in 23 instances. The *B. fragilis* group accounted for 148 (70%) of 212 isolates of anaerobic Gram-negative bacilli. *Bacteroides fragilis* accounted for 78% and *B. thetaiotaomicron* for 14%. Among other species, there were 20 (6%) *Fusobacterium* organisms, 63 (18%) *Clostridium* isolates, and 53 (15%) anaerobic cocci. Seventy-five patients died: 40 of these had *B. fragilis* group isolates (including *B. fragilis*, 28, and *B. thetaiotaomicron*, 8) and 21 had *Clostridium* organisms isolated.

Pathogenesis

Portal of entry

Anaerobic bacteremia is almost invariably secondary to a focal primary infection. As reported for adults [13], the strain of anaerobic organisms recovered depended to a large extent on the portal of entry and the underlying disease. *Bacteroides fragilis* is the most frequent anaerobic isolate [13, 23–28] and, with other members of the *B. fragilis* group species, accounts for 36–64% of anaerobic blood isolates. *Bacteroides thetaiotaomicron* is the second most common member of the group to be isolated from blood. Clostridia, especially *C. perfringens*, and peptostreptococci are also frequently isolated from blood. The gastrointestinal tract accounted for half of the anaerobic bacteremias and the female genital tract was the source of 20% of these bacteremias [13, 27–30].

Brook [25] noted in adults that the gastrointestinal tract was the principal source of *B. fragilis* and clostridial bacteremias and that the female genital tract was the principal source of peptostreptococcal and fusobacterial bacteremias. Redondo *et al*. [30] reported that bacteremias caused by the *B. fragilis* group of organisms originated from: the gastrointestinal tract (69% of bacteremias); soft-tissue wound infections (16%); the female genitourinary tract (5%); and lung infections (4%). Fainstein *et al*. [31] found bacteremia caused by *B. fragilis* to be common in patients with genitourinary and gynecological tumors, acute leukemia, and gastrointestinal malignancies.

The probable portals of entry for the blood culture isolates in the 28 children studied by Brook and associates [17] were: the gastrointestinal (GI) tract (13 patients), the respiratory tract (ear, sinus, and oropharynx, seven), the lower respiratory tract (three), cardiovascular shunts and neurologic shunts (three), and skin and soft tissue (three). When the GI tract was the probable portal of entry, *Bacteroides* sp. (eight isolates, including five *B. fragilis*) and *Clostridium* sp. (four isolates) were the organisms most frequently recovered from blood. The predominant anaerobic organisms recovered in association with infections of the ear, sinus and oropharynx were *Peptostreptococcus* sp. (from four patients) and *F. nucleatum* (from two patients). *Propionibacterium acnes* was grown in cultures taken from four patients, three of whom had artificial cardiac valves or ventriculoatrial shunts. Two of these patients also were initially observed to have meningitis caused by a similar organism. All lower respiratory tract infections that served as a probable source of bacteremia were caused by isolates belonging to the *B. fragilis* group.

No obvious focus of infection was noted in six patients; interestingly, however, all of these patients had some GI problem that might have served as a source of the bacteremia. Furthermore, four of these patients had bacteremia caused by *Clostridium* species.

These findings therefore support studies of adults [13,32,33] and children [6,14] that report that *Bacteroides* species, including the *B. fragilis* group, were the predominant isolates from patients in whom the GI tract was the probable portal of entry. As summarized by Sanders and Stevenson [7], however, other anaerobic Gram-negative bacilli caused bacteremia in children with otitis media and abscesses.

The ear, sinus, and oropharynx were found to be possible portals of entry that predisposed patients to bacteremia with *Peptostreptococcus* sp. and *Fusobacterium* sp. This is not surprising because these organisms are part of the normal flora of these anatomic sites and can be involved in local infections [27].

Three newborns developed bacteremia in conjunction with pneumonia with organisms belonging to the *B. fragilis* group [17]. This has also been noted before in newborns [5] and adults [1]. Although *Bacteroides* accounted for the majority of the episodes of bacteremia in this study, other studies have shown relatively infrequent isolation of these organisms from children [1], except during the neonatal period [5].

An association between surgical procedures and anaerobic septicemia was recently reported. Pass and Waldo [34] observed anaerobic bacteremia in two infants following suprapubic bladder aspiration. *Bacteroides fragilis* was isolated in one instance and in another instance was mixed with *Veillonella alcalescens*. An accidental bowel perforation was the assumed etiology of these infections. Kasik *et al*. [35] observed sepsis and meningitis caused by *E. coli* and *Bacteroides* sp. after anal dilatation. *Fusobacterium mortiferum* was also recovered in the blood.

Fisher *et al*. [36] described bacteremia caused by *B. fragilis* in four of 75 children after elective appendectomy in renal transplant recipients. The bacteremia was associated with profound lymphopenia. Fusobacterial infection generally is associated with otolaryngological processes. Seidenfeld *et al*. [21] reported five patients, four of whom were children, who developed *F. necrophorum* septicemia following oropharyngeal infection. Septicemia caused by *Streptococcus morbillorum* was reported by Rushton to have complicated herpetic pharyngitis [37].

Predisposing factors

Bacteroides fragilis, anaerobic Gram-positive cocci, and *Fusobacterium* sp. were the clinically significant anaerobic organisms most commonly isolated from blood cultures in three recent studies [2–4]. Most of the patients described in these studies were either newborns or were over 6 weeks of age and suffered from chronic debilitating disorders such as malignant neoplasms, immunodeficiencies, chronic renal insufficiency, or decubitus ulcers and carried a poor prognosis. *Bacteroides* sp. were also isolated frequently after perforation of viscus and appendicitis [38,39].

Clostridium sp. may complicate leukemias. Caya *et al*. [40] reported 11 children with leukemia who presented with sepsis caused by *Clostridium septicum* (seven children), *C. perfringens* (two children), and *Clostridium* sp. (two children). None of these children survived the sepsis, which was characterized by thrombocytopenia, gastrointestinal lesions, and neutropenia.

Infectious mononucleosis can also predispose to anaerobic bacteremia. Dagan and Powell [41] observed three patients who developed postanginal anaerobic sepsis following Epstein–Barr virus infection. All three had *Fusobacterium* species isolated (two were *F. necrophorum*) and in one case a *Peptostreptococcus* was also recovered.

Predisposing factors to anaerobic bacteremia in adults include malignant neoplasms [42,43], hematologic disorders [44], transplantation of organs [45], recent gastrointestinal or obstetric gynecologic surgery [43,44,46], intestinal obstruction [47], diabetes mellitus [43], post-splenectomy [42], use of cytotoxic agents or corticosteroids [43], and use of prophylactic antimicrobial agents for bowel preparation prior to surgery [43,46].

Predisposing conditions were noted also in one study of pediatric patients [17]. Two patients had malignant neoplasms, two suffered from hematologic abnormalities, and one had an immune deficiency. Interestingly, 82% of the bacteremias in this series of patients [17] occurred in children who had no immunosuppression or malignant neoplasms. This is in contrast to another study [14] in which anaerobic bacteremia occurred more frequently in children with these predisposing factors. Dental or oral surgery can also predispose to anaerobic bacteremia in adults and children [13,15,16].

Diagnosis and clinical features

The clinical features of anaerobic bacteremia are not much different from those associated with other types of bacteremia in children; however, a relatively longer period is generally needed before an etiologic diagnosis can be made. This can be a result of the smaller volume of blood drawn from children for culture inoculation and the longer time needed for growth and identification of anaerobic organisms.

Diagnosis should include detection of the primary infection. The clinical presentation of anaerobic bacteremia relates, in part, to the nature of the primary infection, which will typically include fever, chills and leukocytosis. Anemia, shock and intravascular coagulation may also be present. *Bacteroides* bacteremia is generally characterized by thrombophlebitis, metastatic infection, hyperbilirubinemia and a high mortality rate (up to 50%). *Clostridium perfringens* bacteremia may have a most dramatic clinical picture, consisting of hemolytic anemia, hemoglobinemia, hemoglobinuria, disseminated intravascular coagulation, bleeding tendency, bronze-colored skin, hyperbilirubinemia, shock, oliguria and anemia. Clostridial bacteria may, however, be transient and inconsequential. However, *C. septicum* infection may be a marker for a silent colonic or rectal malignancy [40].

Blood culture supporting the growth of anaerobic bacteria should be used routinely in all patients. In addition to supporting the growth of strict anaerobes, blood cultures also facilitate the growth of many facultative anaerobes. Some cases of culture-negative endocarditis, fever and systemic toxicity with negative blood cultures are undoubtedly cases of anaerobic bacteremia that elude detection because of inadequate methodology.

Management

Because of the high mortality rate (15–35%) associated with anaerobic bacteremia, it is imperative to establish early effective therapy. Prolonged therapy with antimicrobial agents apparently is adequate for most patients. However, any source of infection, such as an abscess, should be surgically drained. The average duration of therapy in the patients who recovered in one study [17] was 20 days (range, 7–72 days), and the duration of therapy was related to the presence and severity of other infectious sites and complications. Therapy was longest in the treatment of bacteraemia associated with meningitis, wound abscess, sinusitis and empyema. When anaerobes resistant to penicillin, such as the *B. fragilis* group, are suspected or isolated, antimicrobial drugs, such as clindamycin, chloramphenicol, metronidazole, cefoxitin, a carbapenem, or the combination of a beta-lactamase inhibitor and a penicillin (i.e. ticarcillin-clavulante, piperacillin-tazobactam), should be administered. Local surveillance of antimicrobial susceptibility patterns can provide guidelines as to the

choice of the best antimicrobial agent. The development of resistance to all known agents by anaerobes, makes the selection of reliable empirical therapy difficult. Many anaerobic species besides the *B. fragilis* group have acquired the ability to produce beta-lactamase. Rarely, resistance to imipenem, induced by metalloenzymes, and to metronidazole has been reported [48–50]. Consequently, one is not able to predict the susceptibility of some anaerobic isolates. Performing susceptibility testing is of great importance in treating bacteremia caused by anaerobes.

Organisms identical to those causing anaerobic bacteremia can often be recovered from other infected sites (as in 16 patients, 57%, in the study by Brook *et al*. [17]). No doubt these extravascular sites may have served as a source of persistent bacteremia in some cases; however, the majority of patients will recover completely if prompt treatment with appropriate antimicrobial agents is instituted before any complications develop. The early recognition of anaerobic bacteremia and administration of appropriate antimicrobial and surgical therapy play a significant role in preventing mortality and morbidity in pediatric patients.

Preventing bacteremia associated with dental or oral surgery can be accomplished by prophylactic administration of penicillin [51]. It was demonstrated that, although penicillin prophylaxis reduced the total number of facultative anaerobes and strict anaerobes recovered from the blood, metronidazole was more effective in decreasing the recovery of Gram-negative anaerobes [52]. Therefore, a combination of the two may be more effective than either agent alone in eliminating bacteremias after dental procedures.

Complications

The source of anaerobic bacteremia is generally clinically suspected, so therapy with antimicrobial agents active against anaerobes is often instituted empirically. Empirical therapy may provide coverage for anaerobes in only half of the patients with anaerobic bacteremia, and failure to pay attention to the results of anaerobic blood cultures may have serious consequences [53].

Mortality as a result of anaerobic bacteremia remains high. Risk factors for a fatal outcome include compromised status of the host, advanced age, inadequate or no surgical therapy, and the presence of polymicrobial sepsis. Additionally, mortality varies between the infecting *B. fragilis* group species [53,54]. *Bacteroides fragilis* is the most common anaerobic isolate in these studies [53,54], with associated mortality between 24% and 31%, while the mortality associated with *B. thetaiotaomicron* bacteremia ranges between 38% and 100%, and that associated with *B. distasonis* bacteremia is about 50%. Whether these differences are the result of differences in virulence factors such as endotoxins, encapsulation, host defenses, or differences in antimicrobial susceptibility remains unknown.

The mortality following anaerobic bacteremia varies. In one study [17] it was 18% (five of 28 patients) and depended on such factors as age of the patient, underlying disease, nature of the organism, speed of diagnosis, and surgical or medical therapy instituted. This mortality rate is similar to that reported in adults [13]. Of the three infants who died, two were newborns and one was 8 months old. Four patients were infected with organisms of the *B. fragilis* group that were resistant to penicillin; inappropriate antimicrobial therapy was administered to two of these patients, owing to the length of time needed for identification of the organisms, and the other two patients had underlying disorders that further aggravated their condition. The fifth child who died had a ventriculoatrial shunt that was infected with *P. acnes*, in addition to severe hydrocephalus and mental retardation.

Certain other serious concomitant sites of infection can be present in children with anaerobic bacteremia. Most of these sites serve as the source of the infection, however others may represent a site of secondary hematogenous spread of the organism(s). The most frequent conditions are meningitis, peritonitis, subdural empyema, and septic shock. Although some of the children with these infections may become seriously ill, most will respond well to surgical and medical therapy.

In five (18%) of the children included in the report by Brook and co-workers [17], meningitis occurred that was associated with *B. fragilis* (two children), *P. acnes* (two children), and *Peptostreptococcus* species (one child). A direct extension of the organism from an infection site to the meninges might have occurred in two of these children, both of whom had surgical drainage of local collection of pus. One of these children had pansinusitis and required a Caldwell–Luc procedure, where a direct extension of the inflammation to the subdural space through the cribriform plate was demonstrated. Ethmoid drainage and frontal craniotomy yielded pus from the sinus as well as from the subdural space.

Anaerobic organisms recovered from blood were isolated from other infected sites in 16 (57%) of the patients reported by Brook and coworkers [17]. In eight of the 16 patients, anaerobic bacteria were mixed with other anaerobic and/or with aerobic organisms (two to five bacteria/specimen of pus). Extravascular sites from which anaerobic organisms were recovered included abscesses (four patients), cerebrospinal fluid (three patients), peritoneal fluid (four patients), tracheopulmonary aspiration (two patients), sinuses (two patients), and sinus and subdural empyema (one patient). Seven of the eight children who had soft-tissue abscesses or local collections of pus required surgical drainage. Some of these children had recurrent or persistent bacteremia until proper surgical drainage was performed. Four patients also had extravascular collections of pus, however anaerobic organisms were not recovered from these sites, either because anaerobic cultures were not obtained or because the specimens were inappropriately transported.

Shanks and Berman reported two children with multiple pulmonary abscesses who developed hematogenous spread from head and neck infections [55]. *Porphyromonas asaccharolytica* was isolated from the blood of one child, and *B. fragilis* from the other child.

Conclusion

Bacteroides fragilis, *Peptostreptococcus* sp., *Clostridium* sp., and *Fusobacterium* sp. are the most common clinically significant anaerobic isolates causing anaerobic bacteria in children. The strains of anaerobic organisms recovered depended largely on the portal of entry and the underlying disease. Predisposing conditions to anaerobic bacteremia include: neoplasms, immunodeficiencies, chronic renal insufficiency, decubitus ulcers, perforation of viscus and appendicitis, and neonatal age. Organisms identical to those causing anaerobic bacteremia often can be recovered from other infected sites that may serve as a source of persistent bacteremia. When anaerobes resistant to penicillin are suspected or isolated, antimicrobial drugs such as clindamycin, chloramphenicol, metronidazole, cefoxitin, a carbapenem, or the combination of a penicillin and a beta-lactamase inhibitor should be administered. The early recognition of anaerobic bacteremia and administration of appropriate antimicrobial and surgical therapy play a major role in preventing mortality and morbidity in children.

Competing interests

None declared.

References

1. Finegold SM: *Anaerobic bacteria in human disease*. New York, Academic Press, 1977.
2. Chow AW, Guze LB: ***Bacteroidaceae* bacteremia: clinical experience with 112 patients.** *Medicine* 1974, **53**:93-126.
3. Dunkle LM, Brotherton MS, Feigin RD: **Anaerobic infections in children: a prospective study.** *Pediatrics* 1976, **57**:311-320.
4. Thirmuoothi MC, Keen BM, Dajani AS: **Anaerobic infections in children: a prospective study.** *J Clin Microbiol* 1976, **3**:318-323.
5. Brook I, Martin WJ Cherry JD, Sumaya CV: **Recovery of anaerobic bacteria from pediatric patients: a one-year experience.** *Am J Dis Child* 1979, **133**:1020-1024.
6. Chow AW, Leake RD, Yamauchi T, Anthony BF, Guze LB: **The significance of anaerobes in neonatal bacteremia: analysis of 23 cases and review of the literature.** *Pediatrics* 1974, **54**:736-745.
7. Sanders DU, Stevenson J: ***Bacteroides* infections in children.** *J Pediatr* 1968, **72**:673-677.
8. Zaidi AKM, Knaut AL, Mirrett S, Reller LB: **Value of routine anaerobic blood cultures from pediatric patients.** *J Pediatr* 1995, **127**:263-268.
9. Dorsher CW, Rosenblatt JE, Wilson WR, Ilstrup DM: **Anaerobic bacteremia: decreasing rate over a 15-year period.** *Rev Infect Dis* 1991, **13**:633-636.
10. Dorsher CW, Wilson WR, Rosenblatt JE: Anaerobic bacteremia and cardiovascular infections. *Anaerobic Infections and Human Disease*. George WL, Finegold SM (eds). San Diego: Academic Press 1989, 289-310.
11. Lombardi DP, Engleberg NC: **Anaerobic bacteremia: incidence, patient characteristics, and clinical significance.** *Am J Med* 1992, **92**:53-60.
12. Murray PR, Traynor P, Hopson D: **Critical assessment of blood culture techniques: analysis of recovery of obligate and facultative anaerobes, strict aerobic bacteria, and fungi in aerobic and anaerobic blood culture bottles.** *J Clin Microbiol* 1992, **30**: 1462-1468.
13. Morris AJ, Wilson ML, Mirrett S, Reller LB: **Rationale for selective use of anaerobic blood cultures.** *J Clin Microbiol* 1993, **31**: 2110-2113.
14. Echeverria P, Smith AL: **Anaerobic bacteremia observed in a children's hospital.** *Clin Pediatr* 1978, **9**:688-695.
15. Berry FA Jr, Yarbrough S, Yarbrough N, Russell CM, Carpenter MA, Hendley JO: **Transient bacteremia during dental manipulation in children.** *Pediatrics* 1973, **51**:476-479.
16. De Leo AA, Schoenknecht FD, Anderson MW, Peterson JC: **The incidence of bacteremia following oral prophylaxis on pediatric patients.** *Oral Surg* 1974, **37**:36-45.
17. Brook I, Controni G, Rodriguez WJ, Martin WJ: **Anaerobic bacteremia in children.** *Am J Dis Child* 1980, **134**:1052-1056.
18. Beeler BA, Crowder JG, Smith JW, White A: ***Propionibacterium acnes:* pathogen in central nervous system infection.** *Am J Med* 1976, **61**:935-938.
19. Frommell GT, Todd JK: **Polymicrobial bacteremia in pediatric patients.** *Am J Dis Child* 1984, **138**:266-269.
20. Rosenfeld RG, Jameson S: **Polymicrobial bacteremia associated with pharyngotonsillitis.** *J Pediatr* 1978, **93**:251-252.
21. Seidenfeld S, Sutker WL, Luby JP: ***Fusobacterium necrophorum* septicemia following oropharyngeal infection.** *JAMA* 1982, **248**:1348.
22. Givner LB, McGehee D, Taber LH, Stein F, Sumaya CV: **Sinusitis, orbital cellulitis and polymicrobial bacteremia in a patient with primary Epstein–Barr virus infection.** *Pediatr Infect Dis* 1984, **3**:254-256.
23. Caya JG, Truant AL: **Clostridial bacteremia in the non-infant pediatric population: a report of two cases and review of the literature.** *Pediatr Infect Dis* 1999, **18**:291-298.
24. Brook I: **Bacterial infection associated with malignancy in children.** *Int J Pediatr Hematol/Oncol* 1998, **5**:379-386.
25. Brook I: **Anaerobic bacterial bacteremia: 12-year experience in two military hospitals.** *J Infect Dis* 1989, **160**:1071-1075.
26. Gransden WR, Eykyn SJ, Phillips I: **Anaerobic bacteremia: declining rate over a 15-year period [letter].** *Rev Infect Dis* 1991, **13**:1255-1256.
27. Summanen P, Baron EJ, Citron DM, Strong C, Wexler HM, Finegold SM: *Wadsworth anaerobic bacteriology manual*. 5th edn. Belmont, California: Star Publishing Company, 1993.
28. Goldstein EJC, Citron DM: **Annual incidence, epidemiology, and comparative in vitro susceptibilities to cefoxitin, cefotetan, cefmetazole, and ceftizoxime of recent community-acquired isolates of the *Bacteroides fragilis* group.** *J Clin Microbiol* 1988, **26**:2361-2366.
29. Heseltine PNR, Appleman MD, Leedom JM: **Epidemiology and susceptibility of resistant *Bacteroides fragilis* group organisms to new β-lactam antibiotics.** *Rev Infect Dis* 1984, **6(suppl 1)**:S254-259.
30. Redondo MC, Arbo MDJ, Grindlinger J, Snydman DR: **Attributable mortality of bacteremia associated with the *Bacteroides fragilis* group.** *Clin Infect Dis* 1995, **20**:1492-1496.
31. Fainstein V, Elting LS, Bodey GP: **Bacteremia caused by nonsporulating anaerobes in cancer patients. A 12-year experience.** *Medicine (Baltimore)* 1989, **68**:151-162.
32. Mederios AA: ***Bacteroides* bacillemia.** *Arch Surg* 1972, **105**: 819.
33. Washington JA II: **Relative frequency of anaerobes.** *Ann Intern Med* 1975, **83**:908.
34. Pass RF, Waldo B: **Anaerobic bacteremia following bladder aspiration.** *J Pediatr* 1979, **94**:748-750.
35. Kasik JW, Bolam DL, Nelson RM: **Sepsis and meningitis associated with anal dilation in a newborn infant.** *Cl Pediatr* 1984, **23**:509-510.
36. Fisher MC, Balurte HJ, Lang SS: **Bacteremia due to *Bacteroides fragilis* after elective appendectomy in renal transplant recipients.** *J Infect Dis* 1981, **143**:635-638.
37. Rushton A: **Herpetic pharyngitis complicated by anaerobic streptococcal septicemia.** *Cl Pediatr* 1987, **24**:106.
38. Marchildon MB, Dudgeon DL: **Perforating appendicitis: a current experience in Children's Hospital.** *Ann Surg* 1977, **185**: 84-87.
39. Stone JH: **Bacterial flora of appendicitis in children.** *J Pediatr Surg* 1976, **11**:37-42.
40. Caya JG, Farmer SG, Ritch PS, Wollenberg NJ, Tieu TM, Oechler HW, Spivey M: **Clostridial septicemia complicating the course of leukemia.** *Cancer* 1986, **57**:2045-2048.

41. Dagan R, Powell KR: **Postanginal sepsis following infectious mononucleosis.** *Arch Int Med* 1987, **147**:1581-1583.
42. Donaldson SS, Moore MR, Rosenberg SA, Vosti KL: **Characterization of postsplenectomy bacteremia among patients with and without lymphoma.** *N Engl J Med* 1972, **287**:69-71.
43. Bodner SJ, Koenig MG, Goodman JS: **Bacteremic *Bacteroides* infections.** *Ann Intern Med* 1970, **73**:537-544.
44. Alpern RJ, Dowell VR Jr: ***Clostridium septicum* infections and malignancy.** *JAMA* 1969, **209**:385-388.
45. Myerowitz RL, Medeiros AA, O'Brien TF: **Bacterial infection in renal homotransplant recipients: a study of 53 bacteremic episodes.** *Am J Med* 1972, **53**:308-314.
46. Wilson WR, Martin WJ, Wilkowske CJ, Washington JA 2nd: **Anaerobic bacteremia.** *Mayo Clin Proc* 1972, **47**:639-646.
47. Felner JM, Dowell VR Jr: ***Bacteroides* bacteremia.** *Am J Med* 1970, **50**:787-792.
48. Narikawa S, Suzuki T, Yamamoto M, Nakamura M: **Lactate dehydrogenase activity as a cause of metronidazole resistance in *Bacteroides fragilis* NCTC 11295.** *J Antimicrob Chemother* 1991, **28**:47-53.
49. Bandoh K, Ueno K, Watanabe K, Kato N: **Susceptibility patterns and resistance to imipenem in the *Bacteroides fragilis* group species in Japan: a 4-year study.** *Clin Infect Dis* 1993, **16 (suppl 4)**:S382-S386.
50. Rasmussen BA, Bush K, Tally FP: **Antimicrobial resistance in *Bacteroides*.** *Clin Infect Dis* 1993, **16(suppl 4)**:S390-S400.
51. Baltch AL, Pressman HL, Hammer MC, Sutphen NC, Smith RP, Shayegani M: **Bacteremia following dental extraction in patients with and without penicillin prophylaxis.** *Am J Med Sci* 1982, **283**:129-140.
52. Head TW, Bentley KC, Millar EP, deVries JA: **A comparative study of the effectiveness of metronidazole and penicillin-V in eliminating anaerobes from postextraction bacteremias.** *Oral Surg* 1984, **58**:152-155.
53. Brook I: **The clinical importance of all members of the *Bacteroides fragilis* group [letter].** *J Antimicrob Chemother* 1990, **25**:473-474.
54. Chow AW, Guze LB: ***Bacteroidaceae* bacteremia: clinical experience with 112 patients.** *Medicine (Baltimore)* 1974, **53**: 93-126.
55. Shanks GD, Berman JD: **Anaerobic pulmonary abscesses: hematogenous spread from head and neck infections.** *Cl Pediatr* 1986, **25**:520-522.