

# Pediatric Anaerobic Infection

DIAGNOSIS AND MANAGEMENT

SECOND EDITION

ITZHAK BROOK

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# Pediatric Anaerobic Infection

## DIAGNOSIS AND MANAGEMENT

*To my children*  
**Dafna, Dan, Tamar, Yonatan, and Sara**

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# Preface to Second Edition

Since the publication of the first edition of this book in 1983, much has changed in our knowledge and understanding of the role of anaerobic bacteria in infections in children. As more clinicians appreciated the importance of these bacteria, more reports appeared in the literature describing their presence in a variety of infections in pediatric patients. Furthermore, with increased awareness, patient care improved in infections caused by anaerobic bacteria. During this period, newer antimicrobial agents effective against anaerobic bacteria were introduced. Methods of identification of anaerobes improved and were simplified and made easily accessible to most clinicians.

The second edition of the book updates the knowledge about the role of anaerobic bacteria in pediatric infection. New chapters have been added on the virulence of anaerobic bacteria, suppurative genitourinary infection, infected solid tumors and dermal cysts, and synergistic therapy of anaerobic infection. Other topics have been expanded and updated. The subjects added to the second edition include the frequency of isolation of anaerobic bacteria, the role of beta-lactamase-producing bacteria, abdominal infection, osteomyelitis, head and neck infections, and antimicrobial therapy of anaerobic infections.

I am hopeful that practicing physicians will continue to find this textbook useful in delivering care for their patients.

**Itzhak Brook, M.Sc., M.D.**

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# Preface to First Edition

This book was written for physicians who diagnose and treat children with infections. Its purpose is to present—in one volume—the clinical, microbiological, and therapeutic data necessary for the diagnosis and treatment of anaerobic infections in children.

To this end, the book is divided into five parts: Introduction to Anaerobes, Neonatal Infections, Anaerobic Infections of Specific Organ Sites, Other Types of Anaerobic Infections, and Principles of Management. The first part offers background information on anaerobes as normal flora and pathogens, and on laboratory and clinical diagnosis of anaerobic infections. Neonatal anaerobic infections—because they differ from those presenting in older children—are discussed separately in Part II. Parts III and IV, which encompass most anaerobic infections of later childhood, are divided into the following convenient subdivisions within each disease category: microbiological etiology, pathogenesis, diagnosis, management, complications, and, where appropriate, prevention. Part V discusses general principles of treatment. References are provided for those readers interested in more in-depth study.

General books on pediatric infectious disease offer inadequate coverage of anaerobes. Advances in laboratory identification, an increased awareness of the role of anaerobes in childhood, the frustrations of failed attempts to diagnose and treat anaerobic and mixed aerobic-anaerobic infections, and the aforementioned dearth of information on anaerobes available in book form—all prompted the undertaking of this volume. Most of the data herein was derived from clinical and microbiological experience with children. In several instances, however, sufficient data were unavailable in the pediatric literature, and adult data were substituted, which is proof that further work in childhood anaerobic infections is necessary.

I hope that this book will assist physicians and other health care professionals in the treatment of children with infections, and will prompt further studies in the role of anaerobic bacterial infectious diseases.

**Itzhak Brook, M.Sc., M.D.**

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I am most grateful to those who have made this book possible.

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# Contents

## **PART I**

### **INTRODUCTION TO ANAEROBES**

- 1 Anaerobes as normal flora in children, 3
- 2 Collection, transportation, and processing of specimens for culture, 11
- 3 Clinical approach to diagnosis of anaerobic infections, 20
- 4 Anaerobes as pathogens in childhood, 25
- 5 Virulence of anaerobic bacteria, 40

## **PART II**

### **NEONATAL INFECTIONS**

- 6 Introduction to neonatal infections, 81
- 7 Colonization of anaerobic flora in newborns, 53
- 8 Conjunctivitis, 59
- 9 Omphalitis, 61
- 10 Bacteremia and septicemia, 65
- 11 Pneumonia, 72
- 12 Necrotizing enterocolitis, 75
- 13 Ascending cholangitis following porto-enterostomy, 83
- 14 Infections following intrauterine fetal monitoring, 86
- 15 Infant botulism, 92

**PART III**

**ANAEROBIC INFECTIONS OF SPECIFIC ORGAN SITES**

- 16** Central nervous system infections, 101
- 17** Eye infections, 116
- 18** Odontogenic infections, 125
- 19** Ear, nose, and throat infections, 137
- 20** Infections of the head and neck, 181
- 21** Chest infections, 203
- 22** Intraabdominal infections, 225
- 23** Urinary tract infections, 237
- 24** Female genital tract infections, 244
- 25** Skin and soft tissue infections, 253
- 26** Wound and subcutaneous tissue infections, 272
- 27** Infected solid tumors, 278
- 28** Infections of bone and joints, 282
- 29** Clostridial diarrhea and pseudomembranous colitis, 294

**PART IV**

**OTHER TYPES OF ANAEROBIC INFECTIONS**

- 30** Anaerobic bacteremia, 305
- 31** Botulism, 314
- 32** Tetanus, 320
- 33** Burn infections, 330
- 34** Human and animal bite wounds, 336

**PART V**

**PRINCIPLES OF MANAGEMENT**

- 35** Treatment of anaerobic infections, 344
- 36** Beta-lactamase-producing bacteria in mixed infections in children, 364
- Index, 383

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**PART I**

**INTRODUCTION TO  
ANAEROBES**



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## CHAPTER 1

# Anaerobes as normal flora in children

The human body mucosal and epithelial surfaces are covered with aerobic and anaerobic microorganisms.<sup>1</sup> Differences in the environment, such as oxygen tension and pH and variations in the ability of bacteria to adhere to these surfaces, account for changing patterns of colonization. Microflora also vary in different sites within the body system, as in the oral cavity; for example, the microorganisms present in the buccal folds vary in their concentration and types of strains from those isolated from the tongue or gingival sulci. However, the organisms that prevail in one body system tend to belong to certain major bacterial species, and their presence in that system is predictable. The relative and total counts of organisms can be affected by various factors, such as age, diet, anatomic variations, illness, hospitalization, and antimicrobial therapy. However, these sets of bacterial flora, with predictable pattern, remain stable through life, despite their subjection to perturbing factors. Anaerobes outnumber aerobic bacteria in all mucosal surfaces, and certain organisms predominate in the different sites (Table 1-1).

Knowledge of the composition of the flora at certain sites is useful for predicting which organisms may be involved in an infection adjacent to that site and can assist in the selection of a logical antimicrobial therapy, even before the exact microbial etiology of the infection is known. Recognition of the normal flora can also help the clinical microbiology laboratory to choose proper culture media that will be selective in inhibiting certain organisms regarded as contaminants. Furthermore, proper media can be used to enhance the growth of expected pathogens that reside as part of the indigenous flora at the proximity of the infectious site. The usefulness of such information is apparent during investigation of bacteremia of unknown origin, for which the presence of certain organisms can suggest a possible port of entry (i.e. *Clostridium* and *Bacteroides fragilis* usually originate from the gastrointestinal tract).<sup>2</sup>

The normal flora is not just a potential hazard for the host but also a beneficial partner. An example for such synergy is the development of vitamin K deficiency following antimicrobial therapy, which suppresses the gut flora that produce this vitamin. Normal body flora also serve as protectors from colonization or subsequent invasion by potentially virulent bacteria.

## THE SKIN

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The anaerobic microflora of the total body skin usually is made up of the genus *Propionibacterium*.<sup>3</sup> The majority of the isolates of the genus *Propionibacterium* are *Propionibacterium acnes*, while *Propionibacterium granulosum* and *Propionibacterium avidum* can be recovered less frequently. *P. acnes* and *P. granulosum*

**Table 1-1** Normal aerobic and anaerobic flora\*

	Aerobes	Anaerobes	Predominant anaerobic organisms
<b>SKIN</b>			<i>P. acnes</i> <i>Peptostreptococcus</i> sp.
<b>ORAL CAVITY</b>	$10^8-9$	$10^{9-11}$	<i>B. melaninogenicus</i> group <i>Fusobacterium</i> sp.
<b>UPPER GI</b>	$10^{2-5}$	$10^{3-7}$	<i>B. fragilis</i> group
<b>LOWER GI</b>	$10^{5-9}$	$10^{10-12}$	<i>Clostridium</i> sp.
<b>VAGINA</b>	$10^8$	$10^9$	<i>B. bivius</i> <i>B. disiens</i>

\*Number of organisms per 1g secretion or contents

are found on skin with a high sebum content; *P. acnes* is found essentially in all post-pubertal individuals; whereas *P. granulosum* is found regularly in 10% to 20% of individuals and then in numbers about 100-1000 fold fewer than *P. acnes*. The third species, *P. avidum*, is found in the axilla and seems to need conditions with a high availability of water rather than the presence of abundant lipids. Species of *Eubacterium* and *Peptostreptococcus* may also be encountered. The predominant *Peptostreptococcus* is *Peptostreptococcus saccharolyticum*.

These organisms grow within the openings of the sebaceous glands, and consequently, their distribution is proportional to the number of glands, the amount of sebum produced, and the composition of skin surface lipids.<sup>4</sup> In general, the numbers of *P. acnes* on the skin are higher for adults than for young children. Because of their prevalence in the skin and the ear canal, these organisms can contaminate blood cultures and aspirates of abscesses and inner ear fluid.

The occurrence of anaerobic diphtheroids, which were probably *P. acnes*, was studied by Sommerville and Murphy<sup>5</sup> in 22 persons. Considerable variation was noted among the subjects. Sites with mean values of more than  $10^5$  anaerobic diphtheroids per cm of skin were the forehead, presternal area, subclavicular area, midline upper back, and deltoid area. Sites with the fewest organisms ( $<10^3$ /sq cm) were the front and back thighs, shin, dorsum of foot, calf, and forearm. Intermediate counts were obtained in the periumbilical area, scapular area, lower margin of the axilla, sole of the foot, and palm of the hand. Counts of greater than  $10^5$ /sq cm have also been reported for the axilla and the scalp.<sup>6</sup>

## THE ORAL CAVITY

The establishment of the normal oral flora is initiated at birth. Certain organisms such as lactobacilli and anaerobic streptococci, which establish themselves at an early date, reach high numbers within a few days. *Actinomyces*, *Fusobacterium*, and *Nocardia* are acquired by age six months. Following that time, *Bacteroides*, *Leptotrichia*, *Propionibacterium*, and *Candida* also are established as part of the oral flora.<sup>7</sup> *Fusobacterium* populations reach high numbers after dentition and reach maximal numbers at age one year.

The microflora of the oral cavity is complex and contains many kinds of obligate anaerobes. The distribution of bacteria within the mouth seems to be a function

of their ability to adhere to the oral surfaces. The differences in numbers of the anaerobic microflora probably occur because of considerable variations in the oxygen concentration in parts of the oral cavity.

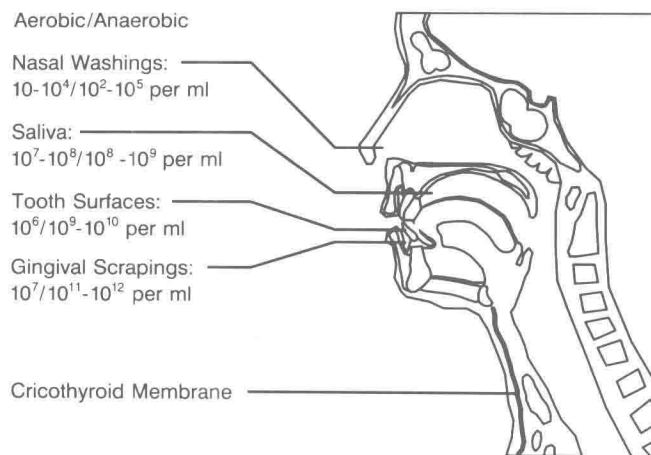
For example, the maxillary and mandibular buccal folds contain 0.4% and 0.3% oxygen, respectively, while the anterior and posterior tongue surfaces contain 16.4% and 12.4%. The gingival sulcus is found to be more anaerobic than the buccal folds, and the periodontal pocket is the most anaerobic area in the oral cavity. The ratio of anaerobic bacteria to aerobic bacteria in saliva is approximately 10:1. The total count of anaerobic bacteria is  $1.1 \times 10^8/\text{ml}$  (Fig. 1-1). The predominant anaerobic bacteria of the anterior nose is *P. acnes*. *F. nucleatum* is the main species of *Fusobacterium* present in the oral cavity. *Bacteroides* species found in the oral cavity include *B. melaninogenicus* group, also known as the black-pigmented *Bacteroides*; *B. gingivalis*; *B. oralis*; *B. oris-buccae* (*ruminicola*); *B. di-siens*; and *B. ureolyticus*.

The number of strains of anaerobes varies. The incidence of *Clostridium* organisms was found to be 10% of the flora of periodontal pockets, 38% in normal gingival crevices, and 44% in carious teeth.<sup>8</sup> *Fusobacteria* also are a predominant part of the oral flora,<sup>9</sup> as are treponemas.<sup>10</sup> *B. melaninogenicus* represent less than 1% of the coronal tooth surface, but constitute 4% to 8% of gingival crevice flora. Veillonellae represent 1% to 3% of the coronal tooth surface, 5% to 15% of the gingival crevice flora, and 10% to 15% of the tongue flora. Microaerophilic streptococci predominate in all areas of the oral cavity, and they reach high numbers in the tongue and cheek.<sup>11</sup> Other anaerobes prevalent in the mouth are *Actinomyces*,<sup>12</sup> anaerobic cocci, *Leptotrichia buccalis*, *Bifidobacterium*, *Eubacterium*, and *Propionibacterium*.<sup>13</sup>

## THE GASTROINTESTINAL TRACT

The gastrointestinal tract becomes contaminated with organisms during the delivery process when the newborn aspirates material from the cervical canal.<sup>14</sup> Early gut colonization with *Bacteroides* sp., *Clostridium* sp., and group B streptococci has been noted more often in infants delivered vaginally than in newborns delivered by cesarean section.<sup>15</sup>

Streptococci, enterococci, and staphylococci usually are present in the first



**Figure 1-1** Concentrations of the microflora of the oral cavity.

days of life. Moreover, even the meconium, the first stool passed, contains bacteria.<sup>16</sup> At the end of the first week of life the fecal flora is predominately anaerobic and contains *Bifidobacterium* sp., *Bacteroides* sp., and *Clostridium* sp. The commonest facultative fecal flora are *Escherichia coli* and *Streptococcus faecalis*.<sup>15</sup>

There also are differences in bacterial flora of breast-fed and formula-fed infants. In breast-fed infants, *Bifidobacterium* becomes the predominant anaerobe.<sup>17</sup> In full-term infants delivered vaginally, *Bacteroides fragilis* was established by the first week in 22% of breast-fed infants as compared to 61% of formula-fed infants.<sup>18</sup> As breast-fed children grow and are weaned, the numbers of *Bifidobacterium* organisms decrease, while the numbers of *Bacteroides* organisms increase until they outnumber *Bifidobacterium* organisms by a ratio of 3:1.

The type of delivery, the dietary constituents, and the gestational age all influence the colonization pattern of anaerobic bacteria.<sup>18</sup> For example, by four to six days virtually all full-term, formula-fed, vaginally delivered infants were colonized by anaerobic bacteria, 61% of the infants harboring *B. fragilis*. In contrast, anaerobes were found altogether in only 59% and *B. fragilis* in 9% of infants delivered by cesarean section, confirming that significant contamination occurred during passage through the birth canal. *Veillonella* organisms were more commonly found in infants delivered by cesarean section. Both premature births and breast feeding were less frequently associated with anaerobe colonization in general, and *B. fragilis* was less likely to be found in breast-fed infants than in their formula-fed counterparts. Studies of newborn infants with congenital small bowel obstruction have established that colonization of the small bowel occurs perorally. In infants with obstruction distal to the ligament of Trietz, a fecal-type flora was found immediately proximal to the site of obstruction, and the distal bowel remained sterile.<sup>19</sup>

The fate of swallowed bacteria and their ability to colonize the gut depends on a number of factors: ability to adhere to mucosa, environmental factors of diet, nutrient availability, chemical and pH conditions, secretory immunoglobulins, intestinal motility, and interference by other bacteria.<sup>20-23</sup>

The stomach, duodenum, jejunum, and proximal ileum normally contain relatively few bacteria. However, the flora becomes more complex, and the number of different bacterial species increase in the distal portion of the gastrointestinal tract.

The stomach is seeded constantly with bacteria from the drainage of nasopharyngeal and salivary secretions and usually contains less than 1000 organisms per milliliter. Only a few of these organisms are anaerobic.<sup>24,25</sup> The low pH of the stomach that is due to its high acid content and the high oxygen tension in the stomach are responsible for the decreased number of organisms that survive in the stomach. The bacterial counts in the small intestine are relatively low, with total counts of  $10^2$  to  $10^5$  organisms/ml. The organisms that predominate up to the ileocecal valve are Gram-positive facultative, while below that structure *Bacteroides* organisms (mostly *B. fragilis*), *Bifidobacterium* organisms, *Lactobacillus* organisms, and coliform bacteria are the major isolates.<sup>26</sup> The mean number of bacteria in the colon is approximately  $10^{12}$  bacteria/gm fecal material. Approximately 99.9% of these bacteria are anaerobic (ratio of aerobes to anaerobes is 1 to 1000-10,000). In the colon 300-400 different species or types of bacteria can be found.

The normal colonic microflora tends to be relatively constant in an individual,<sup>16,27</sup> and constitutes an important defense mechanism against infection. Organisms belonging to the normal flora, such as *B. fragilis*, are capable of protecting against infection by *Salmonella*<sup>28</sup> and *Pseudomonas aeruginosa*.<sup>28a</sup>

Anatomic and physiologic derangement of the gastrointestinal tract can lead to bacterial overgrowth in the upper small bowel.<sup>29</sup> Proliferation of a colonic-type flora in the small intestine may be accompanied by a variety of metabolic disturbances, including steatorrhea, vitamin deficiencies, and carbohydrate malabsorption. Significant increase in the bacterial population in the small bowel was demonstrated in patients with hypochlorhydria and was caused by atrophic gastritis, intake of antacids or cimetidine, or a surgical procedure.<sup>29,30</sup> This has also been observed in patients with ineffective peristalsis,<sup>31</sup> multiple diverticula,<sup>29</sup> cirrhosis, chronic malnutrition, excessive small bowel resection, and abdominal irradiation. Malabsorption of fat is the most common clinical manifestation of bacterial overgrowth and results in steatorrhea and vitamin B<sub>12</sub> deficiency.<sup>29</sup>

The role of the intestinal flora in the induction of systemic or gastrointestinal malignancy has been investigated. However, no clear-cut association has thus far been found.<sup>32</sup> Acute diarrheal illness produces profound alterations in the bacterial populations of the gastrointestinal tract. Under certain conditions the resident microflora is eclipsed by an identifiable pathogen.<sup>33</sup> The rapid transit of diarrheal stool results in a marked reduction in the anaerobic population of the large bowel. In patients with cholera, the concentration of *Bacteroides* in the feces decreases to 10<sup>5</sup> organisms/ml, a reduction of 5 to 6 logs.<sup>32</sup> Apparently, these changes are secondary to the underlying acute process because resolution of diarrhea is accompanied by rapid restitution of the normal flora.

## VAGINAL AND CERVICAL FLORA

The normal vaginal flora is fairly homogeneous. The mean counts of bacteria in the vagina and cervix are approximately 10<sup>8</sup> organisms/ml of secretion (range 10<sup>5</sup> to 10<sup>11</sup>). About 50% of these bacteria are anaerobic.

Studies of the flora of the cervical canal reveal a composition of mixed aerobic and anaerobic flora.<sup>34-38</sup> The aerobic components consist of lactobacilli, group B and D streptococci, *Staphylococcus epidermidis*, *Staphylococcus aureus*, and Gram-negative enteric rods such as *E. coli*.<sup>39</sup>

The anaerobic component consists predominately of lactobacillus and *Peptostreptococcus* sp. *Bacteroides* sp. other than *B. fragilis* group are commonly found in the vagina. *Clostridium perfringens* and other Clostridia may also be found. Different strains of anaerobes were recovered in 49% to 92% of the subjects. *Peptostreptococci* were reported in 7% to 57% of the cultures.

One study reported the predominance of *Peptostreptococcus asaccharolyticus* and *Peptostreptococcus anaerobius*.<sup>37</sup> *Bacteroides* organisms were recovered from most of the cultures; their isolation rates were between 57% and 65%. The predominant strains were *Bacteroides disiens*, *Bacteroides bivius*, *B. melaninogenicus*, *B. fragilis*, and *Bacteroides oralis*.<sup>40</sup> *Veillonella* organisms were recovered from 27%, bifidobacteria species from 10% to 72%, and eubacteria species from 15%. *Clostridium* species were recovered from 17%; these were isolates of *Clostridium bif fermentans*, *C. perfringens*, *Clostridium ramosum*, and *Clostridium difficile*.

Variations in cervical-vaginal flora are related to the effects of age, pregnancy, and menstrual cycle. The microflora in females before puberty, during childbearing years, pregnancy, and after menopause are not uniform. Colonization with lactobacilli is low in children and in postclimactic women, while high in pregnant women and those in their reproductive years. Although differences in colonization between age groups occur in organisms other than *Lactobacillus*, the vaginal flora of children contains many of the aerobic strains recovered from adult women. One study reported the recovery of *B. fragilis* in 24%, *B. melaninogenicus* in 56%,