Clinical Clues to Diagnosis of Anaerobic Infections

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Abstract and Introduction

The diagnosis of anaerobic infections can be difficult, but it may be expedited by the recognition of certain clinical signs. Predisposing conditions and bacteriologic hints should alert the physician, who may apply diagnostic procedures to ascertain the nature of the pathogens and the extent of the infection. Almost all anaerobic infections originate from the patient's own microflora. Poor blood supply and tissue necrosis lower the oxidation-reduction potential and favor the growth of anaerobic bacteria. Any condition that lowers the blood supply to an affected area of the body can predispose to anaerobic infection. Therefore, trauma, foreign bodies, malignancy, surgery, edema, shock, colitis, and vascular disease may serve as predisposing factors. The source of bacteria involved in most anaerobic infections is the normal, indigenous flora. Anaerobic infections can themselves provide clues to the presence of an underlying medical problem.

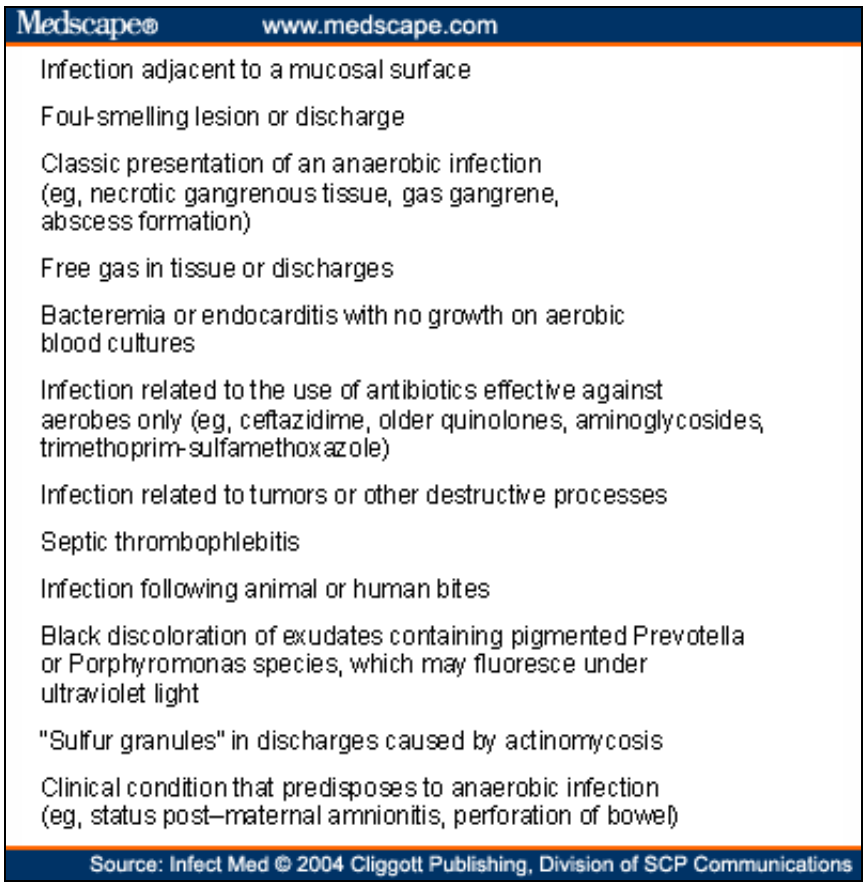
Anaerobic bacteria are the predominant component of the bacterial flora of normal human skin and mucous membranes and are, therefore, a common cause of endogenous bacterial infections. Such infections may be serious and even life-threatening. They can involve all body systems and sites[1] but most often affect the abdominal and pelvic organs, the respiratory system, and the skin and soft tissues. Because of their fastidious nature, anaerobes are difficult to isolate from infectious sites and are often overlooked. Isolation of these organisms when they cause infection is important, since failure to direct therapy against them often leads to clinical failures. Isolating them requires appropriate methods of collection, transportation, and cultivation of specimens.

Treatment of anaerobic bacterial infections is complicated by the slow growth of the bacteria, which typically makes diagnosis in the laboratory possible only after several days; by the often polymicrobial nature of anaerobic infections; and by the growing resistance of anaerobic bacteria to antimicrobial agents.

Clinical and Bacteriologic Signs

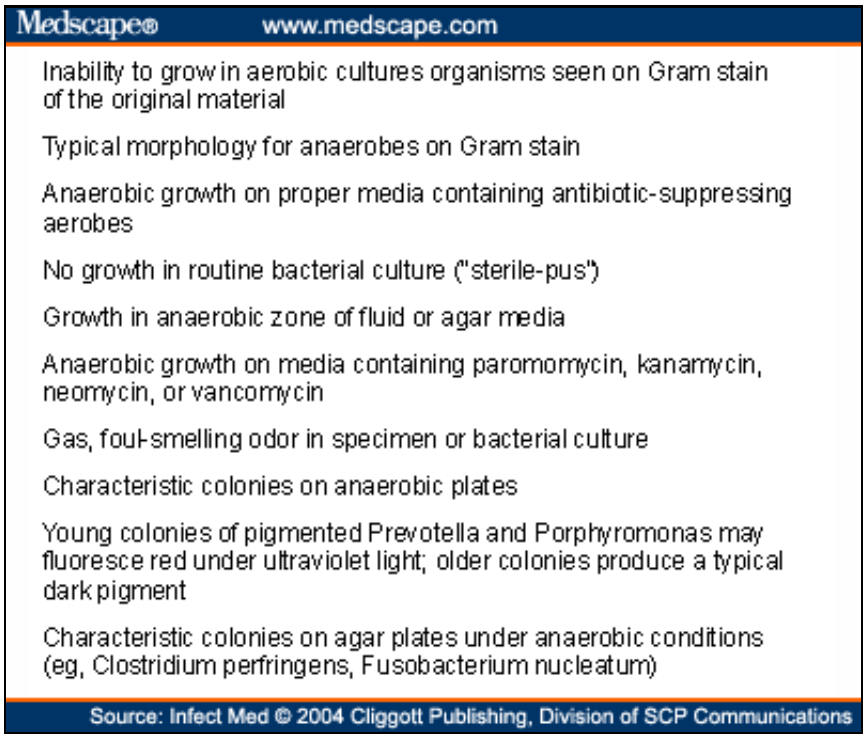
Diagnosis of these difficult-to-iden tify infections is expedited by the recognition of certain clinical signs; these are summarized in . Even though many of these clues are not specific, the presence of several of them in a patient can be suggestive of an anaerobic infection. Predisposing conditions and bacteriologic hints should alert the clinician, who may then apply diagnostic procedures to ascertain the nature of the pathogens and the extent of the infection.

Clues to Diagnosis of an Anaerobic Infection



A number of bacteriologic findings are also suggestive of anaerobic infections; these are listed in . Almost all anaerobic infections originate from the patient's own microflora.

Bacteriologic Findings Suggestive of Anaerobic Infection



Poor blood supply and tissue ne crosis lower the oxidation-reduction potential and favor the growth of anaerobes. Any condition that lowers the blood supply to an affected area can predispose to anaerobic infection. Therefore, presence of a foreign body, malignancy, surgery, edema, shock, trauma, colitis, or vascular disease may predispose one to anaerobic infection.

Previous infection with aerobic or facultatively anaerobic organisms also may make the local tissue conditions more favorable for the growth of anaerobic organisms. Hum an defense mechanisms also may be impaired by anaerobic

conditions.[2]

The source of bacteria involved in most anaerobic infections is the normal, indigenous flora of an individual. The mucosal surfaces of a child become colonized with aerobic and anaerobic flora within a short time after birth.[3,4] Anaerobic bacteria are the most common residents of the skin and mucous membrane surfaces,[5] and they outnumber aerobic bacteria in the normal oral cavity and GI tract at a ratio of 10:1 and 1000:1, respectively.[6] Examples of these mucosal and skin surfaces are the oral, nasal, and sinus cavities; the GI lumen; the conjunctiva; the skin surfaces; and the sebaceous glands. It is not surprising, therefore, that a large proportion of anaerobic bacteria that are part of the normal mucous membrane flora can be recovered from infection that is in proximity to these sites.

The inoculum of organisms that penetrate into a site of injury, such as a human bite or perforated gut, usually is complex and contains a mixture of aerobic and/or anaerobic flora. Although the inoculum of certain organisms that possess greater pathogenicity, such as *Bacteroides fragilis* , can be small initially, such organisms may subsequently become the predominant isolates as the infection progresses.

Anaerobes that are part of the indigenous flora of the oral cavity can be recovered from various infections adjacent to that area, such as infectious cervical lymphadenitis,[7-9] subcutaneous abscesses,[10] and infected burns[10] in proximity to the oral cavity; infected human and animal bites[11]; paronychia[12]; tonsillar and retropharyngeal abscesses[13]; chronic sinus infection[14]; chronic otitis media[15]; periodontal abscess[16]; infectious thyroiditis[17]; aspiration pneumonia[18]; empyema[19]; and bacteremia associated with one of the above infections.[20] The predominant anaerobes recovered from these infections are species of anaerobic gram-negative bacilli (including pigmented *Prevotella* and *Porphyromonas* , *Prevotella oralis* and other *Prevotella* species, and *Fusobacterium*) and gram-positive anaerobic cocci (*Peptostreptococcus* species), which are all part of the normal flora of the mucosal surfaces of the oral, pharyngeal, and sinus cavities ( ).

Recovery of Anaerobic Bacteria in Patients*

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Infection	Peptostrep-tococcus species	Clostridium species	Bacteroides fragilis group	Pigmented Prevotella and Porphyromonas, Prevotella oralis	Prevotella bivia, Prevotella disiens	Fusobacterium species
Blood	1	1	2	1	0	1
CNS	2	1	1	2	0	1
Head and neck	3	1	1	3	0	3
Thoracic	2	1	1	3	0	3
Abdominal	3	3	3	1	1	1
Obstetric-gynecologic	3	2	1	1	2	1
Skin and soft tissue	2	1	2	2	1	1

*Frequency of recovery in anaerobic infections: 0, none; 1, rare (1% to 33%); 2, common (34% to 66%); 3, very common (67% to 100%).

A similar correlation exists in infections associated with the GI tract. Such infections include peritonitis that develops after rupture of the appendix,[21] liver abscess,[22] abscesses and infected burns near the anus,[10] intra-abdominal abscesses,[23] and bacteremia associated with any of these infections.[20] The anaerobes that predominate in these infections are *Bacteroides* species (predominantly the *B fragilis* group), *Clostridium* species (including *Clostridium perfringens*), and *Peptostreptococcus species* .

Another site of infection where a correlation exists between the normal flora and the anaerobic bacteria that are isolated is the genitourinary tract. Infections of the genitourinary tract include amnionitis, septic abortion, and other pelvic infections.[24] The anaerobes usually isolated from these sites are *Prevotella* , *Fusobacterium* , and *Peptostreptococcus* species. Organisms that are part of the vaginal and cervical flora are also important pathogens involved in neonatal infections.

The presence of putrid smell is the most specific clue to an anaerobic infection. The odor is caused by metabolic end-products of the anaerobic organisms, which are mostly organic acids. However, the absence of a foul-smelling discharge does not exclude anaerobic infection, since not all anaerobic bacteria produce it. In deep-seated infections, these odors cannot always be appreciated.

The presence of anoxic conditions can result in the formation of gangrenous necrotic tissue, as in the case of ischemia of an extremity. This anoxic condition predisposes to anaerobic infection, because anaerobes benefit from and proliferate under such conditions.

Gas formation is caused by the metabolic end-products, such as amines and organic acids, released by the multiplying anaerobic organism, and it is enhanced by anoxic conditions. However, some aerobic organisms, such as *Escherichia coli* , also can produce gas in infected tissues. The formation of gas can be detected by palpation or by radiographic examination of the involved area (Figure).

X-ray view of gas gangrene caused by Clostridium septicum infection in a 42-year-old man.

The lack of bacterial growth in aerobic cultures is particularly significant in putrid specimens obtained before administration of antimicrobial therapy. This also can occur in anaerobic bacteremia, in which aerobic blood cultures do not reveal the infecting organisms. An additional clue to the presence of anaerobes could be the presence of bacterial forms in properly prepared Gram-stained specimens in which the aerobic bacterial cultures show no growth. Many laboratories assume that failure to cultivate anaerobes in thioglycolate broth excludes the possibility of an aerobes, but thioglycolate broth inoculated in room air would not provide adequate anaerobic conditions. Furthermore, overgrowth of rapid-growing aerobic organisms, which often are present in mixed infections, may mask the presence of slower-growing anaerobes.

Most anaerobes are susceptible to penicillins, although many anaerobic gram-negative bacilli are resistant to that group of drugs.[25] Other commonly used antibiotics to which almost all anaerobes are resistant are the aminoglycosides and the quinolones. Therefore, persistence or recurrence of an infection in the face of treatment with either of these drug groups (or other antimicrobial agents to which anaerobes are resistant) should arouse suspicion of the presence of anaerobic bacteria in the infection.

Any exposure of a sterile body cavity to indigenous mucosal surface flora can result in infection. Anaerobes are especially common in chronic infections. Certain infections are very likely to involve anaerobes as important pathogens, and their presence should always be assumed. Such infections include brain abscesses, oral or dental infections, infected human or animal bites, aspiration pneumonia, lung abscesses, peritonitis following perforation of a viscus, amnionitis, endometritis, sep tic abortion, tubo-ovarian abscesses, abscesses in and around the oral and rectal areas, and pus-forming necrotizing infections of soft tissue or muscle.

Conditions that decrease the oxidation-reduction potential predispose to anaerobic conditions. These and other general conditions that predispose to anaerobic infection are listed in . Certain malignant tumors, such as colonic, uterine, and bronchogenic carcinomas and necrotic tumors of the head and neck, have the tendency to become in fected with anaerobic bacteria.[26] The anoxic conditions in the tumor and exposure to the endogenous adjacent mucosal flora may predispose to these infections.

Clinical Conditions That Predispose to Anaerobic Infection

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Infection	Peptostrep-tococcus species	Clostridium species	Bacteroides fragilis group	Pigmented Prevotella and Porphyromonas, Prevotella oralis	Prevotella bivia, Prevotella disiens	Fusobacterium species
Blood	1	1	2	1	0	1
CNS	2	1	1	2	0	1
Head and neck	3	1	1	3	0	3
Thoracic	2	1	1	3	0	3
Abdominal	3	3	3	1	1	1
Obstetric-gynecologic	3	2	1	1	2	1
Skin and soft tissue	2	1	2	2	1	1

*Frequency of recovery in anaerobic infections: 0, none; 1, rare (1% to 33%); 2, common (34% to 66%); 3, very common (67% to 100%).

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Newborns, especially those suffering from fetal distress or who are delivered following maternal amniotic infection, are also prone to an aerobic infection. Examples of such infections include the occurrence of neonatal pneumonia after aspiration of infected amniotic fluid[27] and scalp abscess and osteomyelitis caused by the introduction of anaerobic bacteria indigenous to the vaginal-cervical area into the insertion site of the fetal-monitoring needle.[28]

Infections As Clues to Underlying Medical Conditions

An anaerobic infection can itself provide a clue to and warning of an underlying medical problem. For example, a brain abscess may be due to an underlying dental infection, such as periodontitis or periapical abscess, and a lung abscess can be a clue to an underlying bronchogenic malignancy. In fact, malignant disease may first be detected because of

the presence of an anaerobic infection. Malignancy or another process in the colon can induce sepsis with *Clostridium* species (especially *Clostridium septicum*)[29] or arthritis caused by *Eubacterium lentum* ,[30] or it can emerge first as abdominal wall myonecrosis.[31] *Capnocytophaga* , which is a member of the oral microflora, can cause sepsis in patients with leukemia.[32]

Malignancy is often associated with the development of local or systemic anaerobic infections.[26] Systemic infections may reflect compromises in host defenses at several levels. Infections may result from alterations in local conditions at the site of the neoplasm that allow bacteria to gain access to the blood. Humoral immunity; bactericidal plasma action; and the intracellular killing properties of neutrophils, monocytes, and macrophages may be compromised in the presence of a malignancy.[33-36]

The condition in the tumor may predispose to an anaerobic-aerobic infection. Tumors may outgrow their blood supply and become necrotic. The lowered oxygen tension may therefore favor the growth of anaerobic organisms. A tumor can extend into surrounding tissues, causing barrier breakthrough onto mucosal and epithelial surfaces. Alimentary tract inflammatory and focal necrosis can be found in the colonic mucosa in leukemia[37-39] and after cancer chemotherapy.[40]

Another factor underlying the increased susceptibility of patients with cancer to infection and bacteremia is their overall poor nutritional status.[34] An insufficient blood supply in rapidly growing solid tumors can lead to tissue hypoxia, which in turn favors the growth of anaerobes.

Clostridium species possess a selective ability to colonize hypoxic/necrotic areas within malignant tumors. The anaerobic environment within the tumor provides this oxygen-sensitive organism with adequate conditions for proliferation. The current investigative use of nonpathogenic *Clostridium* species to deliver toxic agents to tumor cells takes advantage of this unique physiology.[41]

Anaerobic glycolysis is increased significantly in tumor tissue, with a resulting accumulation of lactic acid in this tissue and its environment. Spores of nonpathogenic *Clostridium* species can localize and germinate in neoplasms and produce extensive lysis of tumors without a concomitant effect on normal tissue.[42] *Clostridium* septicemia originating from an infection within tumor lesions has been reported.[43-46] *C septicum* infection is often associated with the presence of a malignancy that is either known or occult at the time infection occurs. Occult tumors are mostly situated in the cecal area of the bowel. Predisposing conditions for this type of infection include hematologic malignancies, colon carcinoma, neutropenia, diabetes mellitus, and disruption of the bowel mucosa.[47,48]

Bacteremia with gram-negative anaerobic bacilli is also common in patients with solid tumors.[46] Felner and Dowell[49] reported that in 57 (23%) of 250 patients with " *Bacteroides* " (*B fragilis* group, *Fusobacterium* species, and pigmented *Prevotella* species) bacteremia, malignancy was a predisposing condition. The most common malignancies seen in these patients were adenocarcinoma of the colon and uterine or cervical tumors.

Many bacterial infections in adults and children with malignancies are polymicrobial.[46] The bacteria isolated from many of these patients originat ed from the normal flora of the skin or the mucous membrane at or adjacent to the site of the infection.

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