Recently Described Clinically Important Anaerobic Bacteria: Medical Aspects

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There is still inadequate information on the role of certain newly described or reclassified anaerobes in disease processes, on their normal sites of carriage, and on their antimicrobial susceptibilities. Herein, we summarize this information (most of the literature reviewed is from the past 5 years, but a few of the articles are ~10 years old). Porphyromonas species had seemed to be relatively nonpathogenic, but recent work indicates that this belief is incorrect. P. gingivalis, P. levii—like organisms, and P. endodontalis—like organisms have been recovered from a variety of oral and extraoral infections. P. macacae has been recovered from infected cat bite wounds. Sutterella wadsworthensis, recently differentiated from Campylobacter gracilis, has been found in a variety of infections. Bilophila wadsworthia has also been recovered from a wide variety of infections. Newly described anaerobic cocci, gram-positive nonsporeforming rods, and clostridia have also been isolated from various infections.

In recent years, a large number of new or reclassified taxa of anaerobes have been described [1–4]. A number of these anaerobes cause infections in humans and/or animals. Data on the normal sites of carriage of these “new” organisms, on their role in infection, and on their susceptibilities to antimicrobial agents are not readily available. The clinically important anaerobes have recently been reviewed [5]. Herein, we present details on what is known about the anaerobes that have been described more recently. In general, we will follow the outline of a paper on recently described anaerobic organisms [6].

Anaerobic Gram-Negative Rods

Prevotella species. The genus Prevotella is composed primarily of saccharolytic species, both pigmented and nonpigmented, that were previously included in the genus Bacteroides. A recent study by Mätö et al. [7] which dealt with the sources and distribution of P. intermedia and P. nigrescens in clinical samples collected from oral and nonoral infections (table 1), revealed no clear body site—specific clustering of either species although intraabdominal infections more commonly involved P. intermedia, and bacteremia was caused only by P. nigrescens. A faintly pigmented, indole-positive but lipase-negative organism resembling the other two Prevotella species is called P. intermedia/P. nigrescens—like organism or PINLO.

Strains of PINLO have been isolated mainly in oral samples from healthy children and their mothers [8], as well as from odontogenic abscesses, perimplantitis, a pulmonary infection, and a groin abscess (authors’ unpublished data), as summarized in table 1. The nonpigmented Prevotella species are predominantly found in the normal oral and vaginal flora and are isolated as part of a mixed flora from infections related to those sites; however, these organisms are also found in infections related to other sites. P. dentalis is a common isolate recovered from infected root canals [9] and periodontal pockets [10]. It has occasionally been isolated from mandibular and gum abscesses [11] and has been recovered from sialadenitis [12]. The clinical significance of the oral organism P. enoeca is poorly defined.

Some 30%–50% of Prevotella strains from humans are reported to produce β-lactamase, but the true incidence of β-lactamase production is probably significantly higher, as pointed out in the companion paper to this one [6]. One-third to one-half of Prevotella strains are resistant to tetracyclines and ciprofloxacin.

Porphyromonas species. These organisms are found mainly in the indigenous oral flora of humans and animals (and much less often in the gastrointestinal and genitourinary tracts) and have been found in a variety of infections, including human and animal bite infections. P. gingivalis is commonly isolated from periodontitis and less commonly from odontogenic infections; this organism is occasionally isolated from intraabdominal infections such as appendicitis and periappendicitis [7, 13]. P. endodontalis is often associated with root canal infections and has been recovered from odontogenic infections and periappendicular abscesses [14]. Isolates that phenotypically resemble this organism closely (P. endodontalis—like organisms or PELOs) recently have been isolated as part of a mixed flora from extraoral infections in adults (appendicitis with or without periappendicitis, four cases; infected sacral decubitus ulcer, one case; infected mastoid bone, one case; and pilonidal abscess, one case) and have also been isolated in fecal specimens from
children [14]. *P. asaccharolytica* is part of the normal flora in the colon and the vagina and has been recovered from a variety of infections (pleural empyema, peritonitis, perirectal abscess, foot abscess, and toe osteomyelitis) [14].

*P. macacae* is found in the oral cavity of monkeys, cats [15], and dogs and has been found in bite infections (authors’ unpublished data). *P. levii* is found in the rumen of cattle; a phenotypically similar but genotypically different organism (designated *P. levii*–like organism or PLLO) has been recovered from a variety of human infections, primarily soft-tissue infections sometimes involving underlying bone in patients with impaired circulation but also from bacteremia, brain abscesses, and otitis media with mastoiditis [16]. An organism described as *Bacteroides levii* from the normal vaginal flora of pregnant women [17] may belong to the PLLO group. The nonpigmented *P. catoniae* is present on oral mucosal surfaces, in saliva, and in gingival crevices of children and has been recovered from an abdominal abscess in an adult [18].

Most *Porphyromonas* strains isolated from humans are susceptible to penicillin. *P. catoniae* and the animal isolates are more often β-lactamase producers [4, 18]. Five percent to 15% of strains are resistant to clindamycin and ciprofloxacin, and one-third to one-half are resistant to tetracycline, although *M. parvula* are resistant to aminoglycosides and vancomycin; *Leptotrichia* group are resistant to clindamycin and ciprofloxacin, and *Porphyromonas* species are sometimes β-lactamase producers and resistant to aminoglycosides and vancomycin; *Leptotrichia buccalis* is associated with tropical ulcer; this organism is resistant to clindamycin, which is a unique characteristic [24a].

Most strains of *Fusobacterium* are susceptible to penicillin, but production of β-lactamase by *Fusobacterium* is increasingly being reported in the United States [25] and Europe [26]. Fusobacteria are characteristically resistant to erythromycin and related drugs. Ciprofloxacin has only modest activity against fusobacteria, and cephalosporins are generally less active against fusobacteria (other than *F. nucleatum*) than are other agents. *F. mortiferum/varium* strains are somewhat resistant to amoxicillin/clavulanate, and 15%–30% of strains are resistant to clindamycin and tetracycline; cefotaxime and ciprofloxacin are poorly active against this group.

New genera and species after reclassification of *Bacteroides*. As noted by Jousimies-Somer [6], the genus *Bacteroides* now consists mainly of bile-resistant species formerly in the “Bacteroides fragilis group,” although *Prevotella heparinolytica* and *Prevotella zoogloeformans*, which are bile sensitive, cluster with this group. We have recently recovered a strain of *P. heparinolytica* from a patient with pleural empyema [22]. In addition, as noted in the above-cited paper [6], *Tissierella, Catonella morbi,* and *Johnsonella ignava* are being placed in *Clostridium* subphylum clusters. These organisms have rarely been recovered from human clinical infections, and little is known about their susceptibilities to antimicrobial agents.

*Capnocytophaga* of human origin includes two new species, *C. granulosa* and *C. haemolytica*, in addition to *C. ochracea*, *C. gingivalis*, and *C. spitzigera*. These species are common in the oral cavity and have been involved in bacteremia in compromised patients with oral mucositis and other oral lesions [27, 28]. *Leptotrichia buccalis* has also been recovered from compromised bacteremic patients [27]. *Capnocytophaga* and *Leptotrichia* species are sometimes β-lactamase producers and are resistant to aminoglycosides and vancomycin; *Leptotrichia* are resistant to erythromycin as well [27, 28]. A newly proposed species of *Leptotrichia, L. sanguinegens*, has been recovered in blood cultures from four pregnant women, two neonates, and an elderly woman with multorgan failure [29].

*Bacteroides* species of uncertain taxonomic position. *B. ureolyticus* is left over from the previous “*Bacteroides gracilis* group.” *B. ureolyticus* is found in the normal flora of the gastrointestinal and genital tracts and, less often, in the oral cavity. The oral isolates are heterogeneous, and further studies are needed to resolve whether these and isolates from other sites represent more than one species. *B. ureolyticus* has been isolated from various infections including head and neck infections, intraabdominal infections, urogenital infections, and soft-tissue infections; it is found in the oral cavity of monkeys, cats consists mainly of bile-resistant species formerly in the “*Bacteroides fragilis group,*’’ although *Prevotella heparinolytica* and *Prevotella zoogloeformans*, which are bile sensitive, cluster with this group. We have recently recovered a strain of *P. heparinolytica* from a patient with pleural empyema [22]. In addition, as noted in the above-cited paper [6], *Tissierella, Catanella morbi,* and *Johnsonella ignava* are being placed in *Clostridium* subphylum clusters. These organisms have rarely been recovered from human clinical infections, and little is known about their susceptibilities to antimicrobial agents.

*F. necrophorum*, a well-known virulent organism, was the anaerobe most commonly isolated from peritonsillar abscesses in a recent study [23]. *F. alocis, F. sulci,* and *F. periodonticum* are oral organisms often isolated from periodontal pockets [24]. We have isolated *F. russii* from infected bite wounds (especially cat bites), together with *Porphyromonas* species and *Bacteroides tectum*. *F. ulcerans* is associated with tropical ulcer; this organism is resistant to clindamycin, which is a unique characteristic [24a].

<table>
<thead>
<tr>
<th>Type of infection</th>
<th>No. of <em>P. intermedia</em> isolates</th>
<th>No. of <em>P. nigrescens</em> isolates</th>
<th>No. of PINLOs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraabdominal</td>
<td>39</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>Skin and/or soft-tissue</td>
<td>6</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Head and neck</td>
<td>5</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Pleuropulmonary</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Onodontogenic</td>
<td>21</td>
<td>29</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>74</td>
<td>78</td>
<td>9</td>
</tr>
</tbody>
</table>

NOTE. Data are from [7]. PINLO = *P. intermedia/nigrescens*–like organism.
tissue and bone infections. *B. capillosus*, *B. putredinis*, *B. splanchnicus*, *B. coagulans*, and *B. pneumosintes* are among the indigenous flora of the gastrointestinal, genital, and upper respiratory tracts and are occasionally found in infections originating in these sites. A bile-resistant, pigment-producing, saccharolytic organism related to *B. putredinis* and *Rikenella microfusis* has been isolated from inflamed and healthy appendices in children, from the fecal flora of adults and children, and from a perirectal abscess and a brain abscess in a patient with invasive squamous cell carcinoma of the skull with extension to the nasal cavity and orbit [30].

*B. tectum* is of animal origin [15] and may be related to the *Bacteroides fragilis* group but is \( \beta \)-lactamase negative. We have isolated this organism from infected animal bite wound infections in humans. It has also been found, together with *B. pyogenes*, in subgingival sites in dogs with periodontitis [31].

**Campylobacter species.** Most of the oral campylobacters are found in patients with periodontitis. *C. rectus* has been implicated as a putative pathogen at sites of active periodontal breakdown [32] and is seen in cases of appendicitis and its complications [33]. Other campylobacters, such as *C. concisus*, *C. curvus*, and *C. showae* have been isolated from infections of the lung, jaw, and neck, and *C. curvus* has also been isolated from peritoneal fluid [33]. *C. gracilis* is also found in eutrophic infections including head and neck infections, pleural empyema, and appendicitis [33]. *C. gracilis* strains are very susceptible to antimicrobial agents active against anaerobic bacteria. *Sutterella wadsworthensis*. This organism has been isolated primarily from appendicitis, peritonitis, intraabdominal abscesses (including subphrenic abscesses and pelvic abscesses) as well as from a number of different infectious processes including brain abscess, pleural empyema, osteomyelitis (following a dog bite), purulent arthritis, empyema of the gallbladder, and bacteremia ([23, 33] and author’s unpublished data).

Metronidazole resistance is seen in one-third of *Sutterella* strains. Ten percent to 15% of *Sutterella* strains are resistant to piperacillin and piperacillin/tazobactam.

**Bilophila wadsworthia.** *Bilophila wadsworthia* [34] is bile resistant and has been found in the normal fecal flora at counts of \( 10^3 \)–\( 10^7 \)/g (wet weight) of stool in ~60% of individuals [35]. *B. wadsworthia* has also been recovered in 4% of saliva samples and 3% of vaginal samples from humans and from periodontal pockets in three of 16 dogs [35]. *B. wadsworthia* has been found quite frequently in patients with appendicitis and its complications (in our experience, this organism is the third most common anaerobic isolate in such infections), but it is also seen in a wide variety of infections, as noted in table 2. Two of the bilophila infections were in patients with AIDS, and a number of other patients with bilophila infections had various malignancies.

Endotoxic and procoagulant activities have been documented in *Bilophila* [43]. A species-specific oligonucleotide probe for rRNA of *B. wadsworthia* has been developed; it is of potential value in the rapid identification of pure-culture isolates and in the direct identification of the organism in clinical specimens [44]. PCR fingerprinting was performed on two *B. wadsworthia* isolates from the same patient (one isolate was recovered from a cholesteatoma, and the other was recovered from a brain abscess) and documented that they originated from the same clone [36].

Initial studies indicated significant resistance of *B. wadsworthia* to several antimicrobial agents, and \( \beta \)-lactamase activity was not demonstrated. However, a subsequent study, in which triphenyltetrazolium chloride was used to facilitate the reading of endpoints, demonstrated that much of this “resistance” did not exist; however, 87% of 56 strains studied did produce \( \beta \)-lactamase, and spheroplast formation was also demonstrated [45]. Resistance was seen with penicillin G, ampicillin, and amoxicillin and, to a lesser extent, piperacillin; strains that produce \( \beta \)-lactamase should be considered resistant to these agents. Resistance to clindamycin was seen in 2% of strains in this study. Summanen et al. also pointed out that 1% pyruvic acid should be added to the growth medium for susceptibility testing [45].

Another study showed similar results but also demonstrated significant resistance to erythromycin and some resistance to tetracycline [46]. Evidence for bactericidal activity of several agents against *B. wadsworthia* was found in another study [47]; however, only metronidazole was uniformly bactericidal.

<table>
<thead>
<tr>
<th>Reference(s)</th>
<th>Type of infection, site</th>
<th>No. of isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td>[36]</td>
<td>Brain abscess</td>
<td>1</td>
</tr>
<tr>
<td>[36]</td>
<td>Cholesteatoma, ear</td>
<td>1</td>
</tr>
<tr>
<td>[35, 37]</td>
<td>Erosive gingivitis, noma</td>
<td>1</td>
</tr>
<tr>
<td>[35]</td>
<td>Pleural empyema</td>
<td>1</td>
</tr>
<tr>
<td>[35]</td>
<td>Pericardial fluid</td>
<td>1</td>
</tr>
<tr>
<td>[38]</td>
<td>Breast abscess</td>
<td>1</td>
</tr>
<tr>
<td>[39, 40]</td>
<td>Liver abscess</td>
<td>2</td>
</tr>
<tr>
<td>[39]</td>
<td>Intraabdominal abscess</td>
<td>3</td>
</tr>
<tr>
<td>[35, 39–42]</td>
<td>Bacteremia</td>
<td>7</td>
</tr>
<tr>
<td>[39, 40]</td>
<td>Biliary tract infection</td>
<td>6</td>
</tr>
<tr>
<td>[35, 40]</td>
<td>Fournier’s gangrene</td>
<td>2</td>
</tr>
<tr>
<td>[40]</td>
<td>Necrotizing fascitis, other</td>
<td>1</td>
</tr>
<tr>
<td>[35]</td>
<td>Hidradenitis suppurativa</td>
<td>1</td>
</tr>
<tr>
<td>[39]</td>
<td>Cellulitis</td>
<td>1</td>
</tr>
<tr>
<td>[35, 40]</td>
<td>Soft-tissue abscess</td>
<td>4</td>
</tr>
<tr>
<td>[35, 40]</td>
<td>Infected decubitus and diabetic foot ulcers</td>
<td>3</td>
</tr>
<tr>
<td>[35]</td>
<td>Osteomyelitis</td>
<td>2</td>
</tr>
<tr>
<td>[39]</td>
<td>Endometritis</td>
<td>1</td>
</tr>
<tr>
<td>[35]</td>
<td>Vaginal discharge</td>
<td>1</td>
</tr>
<tr>
<td>[39]</td>
<td>Anal and perianal abscess</td>
<td>3</td>
</tr>
<tr>
<td>[40]</td>
<td>Bartholinitis, abscess</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>44</td>
</tr>
</tbody>
</table>
Chloramphenicol and clindamycin showed poor bactericidal activity, and imipenem, ampicillin/sulbactam, ticarcillin/clavulanate, and cefoxitin had intermediate activity.

Selected motile gram-negative anaerobic rods. Most of the motile anaerobic gram-negative bacilli are relatively fastidious and are not recovered often in clinical microbiology laboratories. Various Selenomonas species are found in subgingival sites in patients with periodontitis [48]. Anaerobiospirillum succiniciproducens has been recovered from cultures of blood from immunocompromised patients and in feces from patients with diarrhea. A. succiniciproducens is prevalent in the fecal flora of cats and dogs, and a zoonotic role has been proposed [49]. Desulfovibrio desulfuricans, Desulfomonas pigra, Succinivibrio dextrinisolvens, and Butyribivibrio fibrisolvens (recently reclassified within a Clostridium subphylum, cluster XIVa) have occasionally been recovered from clinical infections [50] (this reference provides detailed susceptibility data). A case of pyogenic liver abscess from which a probable new species of Desulfovibrio was isolated has been described recently [51]. The patient had previously had cholelithiasis requiring cholecystectomy; the organism was isolated both from the liver abscess contents (together with F. varium) and from the blood (Desulfovibrio could not be subcultured from the blood culture bottle).

Enterotoxin-producing B. fragilis. Enterotoxin-producing strains of B. fragilis have been implicated in self-limited diarrheal disease, particularly in children 1–5 years of age [52].

Anaerobic Gram-Positive Bacteria

Anaerobic gram-positive cocci. There are four newly-described species of Peptostreptococcus. P. hydrogenalis has been recovered from the human fecal and vaginal flora [53], P. vaginalis from the human vagina [54], P. lacrimalis from the human eye [54], and P. lactolyticus is from an unknown source [54]. The clinical significance of all these organisms is unknown. Staphylococcus saccharolyticus has occasionally been isolated from clinical specimens including blood cultures (author’s unpublished data).

Streptococcus species. The streptococci of the Streptococcus milleri group (S. anginosus, S. constellatus, and S. intermedius) as well as Gemella morbillorum, are actually microaerophilic. They are found with some frequency in clinical infections of all types, and they are commonly isolated in pure culture [55].

Nonsporeforming anaerobic gram-positive rods and clostridia. Some “CDC (Centers for Disease Control and Prevention) coryneform bacteria” have now been assigned to the genus Actinomyces. CDC group 1 coryneform bacteria are now A. neuii (there are two subspecies, neuii and anitratbus) [56], CDC coryneform group 2 bacteria are now A. bernardiae [57], and CDC coryneform group E (also called A. pyogenes-like) are now classified in two new species, A. radingae and A. turicensis [58]. Neither A. neuii nor the A. radingae-A. turicensis complex cause typical actinomycosis. A. neuii represented 17% of all Actinomyces strains isolated in a 4.5-year period at one laboratory [59].

In general, the two subspecies of A. neuii produce similar infections: abscesses (mainly axillary and inguinal furuncles and breast abscess), infected atheroma, diabetic foot ulcers, other cutaneous ulcers, cellulitis, prostatitis, urinary tract infection, infected amniotic fluid, and bacteremia. A number of patients with these infections were immunosuppressed, and there were a number of recurrences of abscesses. One of the seven patients with bacteremia (associated with purulent arthritis of a hip) died [59]. A study of 67 strains of A. neuii revealed that they were all susceptible to penicillin G, clindamycin, erythromycin, vancomycin, and rifampin and that they were commonly resistant to ciprofloxacin and gentamicin and occasionally resistant to tetracycline [59].

There is only a small amount of clinical information concerning A. bernardiae. The clinical diagnosis or source of seven strains studied by Funke et al. [57] were blood (three isolates), chest abscess, ear abscess, abscess, and eye infection.

In the previously cited study [59], the authors found that 61% of their Actinomyces isolates during the above-noted 4.5-year period were in the A. radingae-A. turicensis complex. This complex has been recovered from a variety of infectious processes including otitis, pleural empyema, infected decubitus ulcers, and perianal abscesses [58]; from a subcutaneous abscess and a diabetic foot ulcer complicated by bacteremia (the organism was present in both specimens) [60]; and from an intraabdominal abscess, appendicitis with peritonitis, cholecystitis, diverticulitis, cystitis, otitis media, mastoiditis, and bacteremia [61].

A. bernardiae and A. pyogenes have recently been placed in the genus Arcanobacterium [62]. Schaal and Lee [63] have reviewed the role of the previously known species of Actinomyces in classic actinomycosis and a variety of other types of infection.

Eubacterium sensu stricto and the related organism Pseudoramibacter alactolyticus (previously Eubacterium alactolyticum) are reclassified in Clostridium cluster XV [64]. Pseudoramibacter alactolyticus has been isolated from dental calculus and the gingival crevices of patients with periodontal disease, root canal infection, and oral abscesses; P. alactolyticus has been isolated from various other infections including brain abscesses, lung abscesses, pleural empyema, jugal cellulitis, postoperative wound infections, and abscesses related to the intestinal tract [64]. The 25 strains studied were susceptible to chloramphenicol (MIC, 12 μg/mL), clindamycin (MIC, 1.6 μg/mL), erythromycin (MIC, 3 μg/mL), penicillin G (MIC, 2 U/mL), and tetracycline (MIC, 6 μg/mL) [64]. There are a number of oral asaccharolytic Eubacterium species that have been recovered from patients with periodontitis [65, 66]. One of the newly described species, Eubacterium exiguum, has been isolated from necrotic human pulp samples, periapical infections, and acute periodontal abscesses [65].
Bifidobacteria and lactobacilli are seldom involved in clinical infections, but it is important to realize that lactobacilli are occasionally recovered from blood cultures and may pose a problem since many lactobacilli are resistant to vancomycin [67].

An unusual, multicellular, spirally aggregated Clostridium strain was isolated from the blood drawn from a patient with probable chronic lymphocytic leukemia [68]. This organism was tested for susceptibility to antimicrobial agents with use of the Etest (AB BIODISK, Solna, Sweden) and was found to be quite susceptible to penicillin G, cefotaxime, imipenem, and metronidazole but marginally susceptible to clindamycin and cefoxitin. Clostridium ramosum, Clostridium innocuum, and Clostridium clostridioforme are often isolated from significant infections in humans. The antimicrobial susceptibility of some 20 strains of each of these species was studied and compared with 11 strains of Clostridium perfringens by using the Wadsworth agar dilution procedure [69]. All strains of C. perfringens were susceptible to all 11 antimicrobial agents studied. In the case of C. ramosum, 20% of strains were resistant to penicillin, cefoxitin, and cefotetan, and 5% were resistant to clindamycin. All strains of C. innocuum were resistant to cefoxitin and cefotetan; many strains were resistant to penicillin G, a number were relatively resistant to vancomycin, and occasional strains were resistant to clindamycin. Over 90% of strains of C. clostridioforme were penicillin resistant (although only one produced β-lactamase), and occasional strains were resistant to piperacillin/tazobactam.

References