Intradermal skin tests and complement fixation serologic tests for donovanosis lack sufficient sensitivity and specificity and are not routinely performed in clinical practice.[4] A sensitive and specific indirect immunofluorescence serologic test has been developed using tissue sections from proven cases of donovanosis as the antigen.[44] However, a lack of suitable clinical material that may be used as the antigen limits widespread use of this test. The ability to culture *K. granulomatis* in monocytes[9,45] and Hep-2 cells[10] may ultimately lead to the development of additional serologic tests in the future and offers the possibility of developing in vitro antimicrobial susceptibility testing of clinical isolates to generate more rational therapeutic decision-making approaches.

Using DNA extracted from biopsy material, Australian researchers demonstrated a high degree of molecular homology between *K. granulomatis* and other *Klebsiella* spp. by sequencing a region of the *phoE* (phosphatase porin) gene of *K. granulomatis*.[46] Although there appears to be a high degree of homology between *phoE* genes of *K. granulomatis* and other *Klebsiella* spp., researchers were able to amplify a 700-bp region demonstrating two base changes that occur only in *K. granulomatis,* thereby differentiating it from other *Klebsiella* spp. This product was subsequently digested with the *Hae*III restriction endonuclease to yield a 167-bp fragment unique to *K. granulomatis*.[47] This molecular approach was later refined to include a colorimetric detection system.[48,49] This work offers a foundation for development of future diagnostic methods for donovanosis and may ultimately provide a viable routine alternative to culture or microscopy.

THERAPY

Prompt initiation of antimicrobial therapy slows progression of lesions and limits further tissue destruction. However, there is no global consensus about the ideal treatment for donovanosis because most antibiotics have been evaluated in open trials, with few data available from comparative, microbiologically controlled studies. Azithromycin (1 g once per week orally or 500 mg daily orally for at least 3 weeks) is now endorsed as the first-line recommended agent by US and European treatment guidelines based on successful outcomes in numerous cases series and individual case reports.[3,50] The optimal duration of treatment cannot be stated categorically because larger lesions appear to require a longer duration of therapy.

With successful therapy, lesions begin to heal from the edges toward the center. Experts suggest that treatment should be continued until complete epithelialization has occurred, which can take several weeks; otherwise relapse may occur. Historically, tetracycline (500 mg four times daily orally) or doxycycline (100 mg twice daily orally) were the treatments of choice for the disease, although many treatment failures or relapses were recorded.[51] Similarly, trimethoprim-sulfamethoxazole (trimethoprim 80 mg/sulfamethoxazole 400 mg, two tablets twice daily orally) proved effective in many cases, but relapse was common (presumably due to inadequate duration of treatment).[4,13] Erythromycin (500 mg four times daily orally) has also been used extensively, especially in pregnancy (with or without the addition of an aminoglycoside such as gentamicin).[4,15] However, gastrointestinal side effects are commonly reported.

Studies of azithromycin demonstrate its clinical effectiveness,[52] although randomized controlled trials are lacking. Outcomes data indicate that 1 g taken orally weekly for 4 to 6 weeks may be the most effective strategy.[53] This antibiotic may be particularly appropriate for the treatment of donovanosis because it concentrates within macrophages and exhibits a long tissue half-life. An added advantage of azithromycin is that it may also have activity against other sexually transmitted bacteria—notably *Haemophilus ducreyi, Treponema pallidum,* and *C. trachomatis.* Other medications that have proved effective include quinolone antibiotics,[54] chloramphenicol and thiamphenicol,[55] ceftriaxone,[56] and the aminoglycosides gentamicin and streptomycin, which have often been used to supplement tetracycline therapy in severe cases.[55,57] In contrast, penicillin appears to be ineffective for treatment of the disease. Anecdotal evidence suggests that lesions may be more extensive and that prolonged periods of therapy may be required for patients with donovanosis who are coinfected with human immunodeficiency virus.

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236 Other Gram-Negative and Gram-Variable Bacilli

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SHORT VIEW SUMMARY

Definition
- This chapter includes gram-negative and gram-variable aerobic bacilli that are less commonly encountered as causes of infection and are not discussed in other chapters.
- The taxonomy of many of these organisms has been and continues to be in a state of flux.
- The organisms discussed are broadly divided into those that ferment glucose and those that weakly ferment or do not ferment glucose. Specific genera discussed include the glucose fermenters (*Actinobacillus* and *Aggregatibacter, Aeromonas, Cardiobacterium, Chromobacterium, Dysgonomonas, Kingella,* zoonotic *Neisseria* species, *Plesiomonas*), and the glucose nonfermenters and weak fermenters (*Achromobacter* and *Alcaligenes, Chryseobacterium* and *Elizabethkingia, Comamonas* and *Delftia, Eikenella, Flavobacterium* and *Myroides, Ochrobactrum, Oligella,* less common species of *Pseudomonas, Ralstonia* and *Cupriavidus, Rhizobium, Roseomonas, Shewanella, Sphingobacterium, Sphingomonas,* and *Weeksella* and *Bergeyella,* as well as Centers for Disease Control and Prevention Groups NO-1, WO-1, WO-2, O-1, O-2, and O-3 and *Gardnerella* and *Mobiluncus*).

Epidemiology
- Some of these gram-negative bacilli are ubiquitous in the environment.
- Many are generally considered to be of low virulence but may be opportunistic pathogens under certain circumstances.
- Some infections have been linked to hospital sources, particularly unclean water sources, nonsterile environmental surfaces, or contaminated solutions.

Microbiology
- Many of these organisms are fastidious and difficult to grow.
- Identification of glucose-nonfermenting gram-negative bacilli poses a challenge to clinical laboratories because conventional biochemical systems frequently fail to provide accurate identification. Accurate identification, especially to species level, often requires cell wall fatty acid analysis, 16S ribosomal RNA gene sequencing–based technologies, or matrix-assisted laser desorption/ionization time-of-flight mass spectrometry.

Diagnosis
- The types of infections caused by these organisms are quite varied and are diagnosed by analysis of cultures of samples obtained from the infection site.
- Because these organisms are infrequently encountered and are often of low virulence, interpretation of culture results must be correlated with clinical findings.

Therapy
- The small number of patients reported and the variety of antibiotic regimens used do not permit identification of the optimal therapeutic regimen for most of these organisms.
- Methods for antibiotic susceptibility testing for many of these organisms are not standardized and Clinical and Laboratory Standards Institute breakpoints for interpretation may not be available.
- Some of the environmental bacteria are of concern because they carry resistance genes on transferable genetic elements and could serve as reservoirs of resistance genes when introduced into the clinical setting.
- Some of these infections may be difficult to eradicate when the causal bacteria exist in well-developed biofilms.

Prevention
- Attention should be given to practices to prevent device-related infections, particularly in immunocompromised individuals.

A large number of gram-negative aerobic bacilli have been reported to cause human infection. In this chapter, selected gram-negative and gram-variable organisms are discussed that have not been described in other chapters and are important in certain clinical or epidemiologic circumstances, are newly described, or present special problems of diagnosis or therapy. For some of the bacteria considered here, taxonomy is in a state of flux as classifications based on phenotypic characteristics are replaced by contemporary measures of genetic relationship, including 16S ribosomal RNA (rRNA) sequencing studies. Current nomenclature and previous designations are listed in Table 236.1.

Identification of some of these organisms is difficult; the automated systems used by many microbiology laboratories cannot identify some of these bacteria and often misidentify others. Consequently, clinical laboratories sometimes use a general description (e.g., gram-negative nonfermenter) rather than the genus and species name. The clinical site of infection (as shown in Table 236.2), colony morphology, and the ability of the organism to metabolize carbohydrates by fermentation provide clues that can suggest a particular organism or group of organisms. This information can help select the most effective way to provide definitive identification because for some of these organisms, special procedures for recovery, characterization, or antimicrobial susceptibility testing are required. The decision to use alternative diagnostic methods is often based on the perceived clinical significance of the isolate, economic considerations, and available expertise. Cell wall fatty acid analysis and molecular methods, such as 16S rRNA gene sequencing, have been used to identify difficult organisms, but these methods are not available in most clinical laboratories. The introduction of matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry for identification of microorganisms in clinical laboratories may overcome some of the limitations of biochemical-based identification and allow for identification of microorganisms that are difficult to identify using traditional biochemical methods.

Because complete identification is often not pursued, infections caused by some of these uncommon pathogens may go unrecognized. In addition, there are no published methodologic guidelines or interpretive breakpoints for susceptibility testing for most of these organisms. Consequently, reported susceptibility test results from the literature can be difficult to interpret, especially if methods and interpretive criteria are not specified. For susceptibility testing of organisms for which there are no US Food and Drug Administration or Clinical and Laboratory Standards Institute (CLSI) interpretive breakpoints, microbiology reports are generally limited to the minimal inhibitory concentration (MIC) value, and an interpretation is not provided.

GLUCOSE FERMENTERS

Actinobacillus and *Aggregatibacter* Species

Actinobacillus and *Aggregatibacter* species are coccoid to small gram-negative bacilli in the family Pasteurellaceae. These organisms are normal microbiota of the oral cavity, and less frequently the urogenital tract,

TABLE 236.1 Current Nomenclature and Previous Names of Gram-Negative Bacteria

CURRENT DESIGNATION	PREVIOUS NAMES
Glucose Fermenters	
Actinobacillus spp. *A. ureae*	*Pasteurella ureae, Pasteurella haemolytica* var. *ureae*
Aeromonas spp. *A. hydrophila* *A. caviae* *A. veronii* biotype *sobria*	*A. sobria*
Aggregatibacter actinomycetemcomitans	*Actinobacillus actinomycetemcomitans, Bacterium actinomycetemcomitans*
Cardiobacterium spp. *C. hominis* *C. valvarum*	
Chromobacterium violaceum	
Dysgonomonas capnocytophagoides	CDC DF-3
Kingella spp.	
Neisseria animaloris, Neisseria zoodegmatis	CDC EF-4a, CDC EF-4b
Plesiomonas shigelloides	*Aeromonas shigelloides, Pseudomonas shigelloides*
Glucose Nonfermenters (or Weak Fermenters)	
Achromobacter spp. *A. xylosoxidans* *A. denitrificans*	*Alcaligenes denitrificans* subsp. *xylosoxydans, Alcaligenes xylosoxidans* subsp. *xylosoxidans, Alcaligenes xylosoxidans* *Alcaligenes denitrificans, Alcaligenes xylosoxidans* subsp. *denitrificans*
Alcaligenes faecalis	*A. odorans,* CDC VI
Bergeyella zoohelcum[a]	*Weeksella zoohelcum,* CDC IIj
Chryseobacterium spp. *C. indologenes*	*Flavobacterium indologenes*
Comamonas spp. *C. testosteroni*	*Pseudomonas testosteroni*
Cupriavidus spp.[b] *C. pauculus* *C. gilardii*	*Wautersia paucula, Ralstonia paucula,* CDC group IVc-2 *Wautersia gilardii, Ralstonia gilardii*
Eikenella corrodens	*Bacteroides corrodens*
Elizabethkingia meningoseptica[c]	*Chryseobacterium meningosepticum, Flavobacterium meningosepticum*
Methylobacterium mesophilicum and *M. extorquens*[d]	*Pseudomonas mesophilica*; *Protomonas extorquens, Vibrio extorquens, Bacillus extorquens, Pseudomonas extorquens, Flavobacterium extorquens, Protaminobacter rubra,* "the pink phantom"
Myroides spp. *M. odoratus* *M. odoratimimus*	*Flavobacterium odoratum*
Ochrobactrum spp. *O. anthropi* *O. intermedium*	CDC Vd, *Achromobacter* groups A and D *Achromobacter* group C
Oligella spp. *O. ureolytica* *O. urethralis*	CDC IVe *Moraxella urethralis,* CDC M-4
Pseudomonas spp. *P. fluorescens* *P. putida* *P. stutzeri* *P. oryzihabitans* *P. luteola*	*Flavimonas oryzihabitans, Chromobacterium typhiflavum,* CDC Ve-2 *Chryseomonas luteola, Chryseomonas polytrichia,* CDC Ve-1
Ralstonia spp. *R. pickettii* *R. mannitolilytica*	*Pseudomonas pickettii, Burkholderia pickettii* *R. pickettii* biovar 3/"*thomasii,*" *Pseudomonas thomasii*
Rhizobium radiobacter	*Agrobacterium radiobacter, Bacillus radiobacter, Bacterium radiobacter, Rhizobium radiobacter, Achromobacter radiobacter, Alcaligenes radiobacter, Pseudomonas radiobacter, Agrobacterium tumefaciens,* CDC Vd-3
Roseomonas spp.	CDC pink coccoid groups I through IV
Shewanella putrefaciens	*Pseudomonas putrefaciens, Alteromonas putrefaciens, Achromobacter putrefaciens,* CDC Ib-1, Ib-2
Sphingobacterium spp. *S. multivorum* *S. spiritivorum*	*Flavobacterium multivorum,* CDC IIk-2 *Flavobacterium spiritivorum,* CDC IIk-3
Sphingomonas paucimobilis	*Pseudomonas paucimobilis,* CDC IIk-1
Weeksella virosa	*Flavobacterium genitale,* CDC II-f

[a]See "*Weeksella* and *Bergeyella* Species" in text.
[b]See "*Ralstonia* and *Cupriavidus* Species" in text.
[c]See "*Chryseobacterium* and *Elizabethkingia* Species" in text.
[d]See "*Roseomonas* Species and Other 'Pink-Pigmented' Gram-Negative Bacilli" in text.
CDC, Centers for Disease Control and Prevention.

TABLE 236.2 Classification of Selected Gram-Negative Aerobic Bacilli by Likely Site of Infection

	MOST LIKELY CLINICAL SETTINGS AND SITES OF INFECTION								
ORGANISM	**Bloodstream**	**Device Associated**	**Intestine**	**Soft Tissue**	**Osteoarticular**	**Bite Wound**	**Urine**	**CSF**	**Nosocomial Clusters**
Glucose Fermenters									
Aeromonas	X		X	X					
Aggregatibacter	X			X		X			
Cardiobacterium	X								
Chromobacterium	X			X					
Dysgonomonas			X						
Elizabethkingia	X							X	X
Kingella	X				X				
Neisseria animoralis, N. zoodegmatis (CDC group EF-4)						X			
Plesiomonas			X						
Glucose Nonfermenters (or Weak Fermenters)									
Achromobacter	X	X							X
Bergeyella						X			
Chryseobacterium	X						X		X
Comamonas	X							X	X
Cupriavidus	X								
Eikenella	X			X	X	X			
Methylobacterium	X	X							
Myroides	X								X
Ochrobactrum	X	X							X
Oligella							X		
Pseudomonas	X	X							X
Ralstonia	X								X
Rhizobium	X	X							
Roseomonas	X	X							
Shewanella	X			X					X
Sphingobacterium	X								
Sphingomonas	X	X						X	
Weeksella							X		

CDC, Centers for Disease Control and Prevention; *CSF,* cerebrospinal fluid.

in humans. They also colonize animals, which can serve as reservoirs for opportunistic human infections. The genus *Aggregatibacter* was created based on the phylogenetic similarity of *Actinobacillus actinomycetemcomitans* and *Haemophilus aphrophilus, Haemophilus paraphrophilus,* and *Haemophilus segnis.*[1] On transfer to the new genus, *Aggregatibacter aphrophilus* and *Aggregatibacter paraphrophilus* were combined into one species, *Aggregatibacter aphrophilus.*[1] The genus name reflects a propensity of these organisms to aggregate with other bacteria.

Aggregatibacter actinomycetemcomitans (formerly *Actinobacillus actinomycetemcomitans*) is the best known pathogen of this group. *A. actinomycetemcomitans* was first described as a human pathogen in 1912 and was initially called *Bacterium actinomycetem comitans.* Early isolates were recovered only in conjunction with *Actinomyces israelii* (hence the species designation), leading to speculation that *A. actinomycetemcomitans* was not itself capable of causing disease. After the introduction of penicillin, it was observed that *A. actinomycetemcomitans* sometimes could be recovered from persistent lesions of actinomycosis after *A. israelii* was eradicated. By the early 1960s, recovery of this organism in pure culture from blood and other normally sterile body fluids was reported widely. The organism is best known as a cause of endocarditis but has also been isolated in pure culture from patients with meningitis, brain abscess, endophthalmitis (with and without concomitant endocarditis), soft tissue infections, parotitis, septic arthritis, osteomyelitis, spinal epidural abscess, urinary tract infection, pneumonia, empyema, and pericarditis.[2,3] Soft tissue infections most commonly involve the cervicofacial area, although they can occur elsewhere, including the chest and abdomen. There are reports of *A. actinomycetemcomitans* mimicking actinomycosis and causing pneumonia with chest wall invasion.[4]

Although the organism is part of the endogenous microbiota of the mouth and can be recovered from about 20% of teenagers and adults, it (along with *Porphyromonas gingivalis*) is one of the major pathogens in adult and juvenile forms of periodontitis. Extraoral infections are believed to occur due to hematogenous dissemination from lesions in the oral cavity. *A. actinomycetemcomitans* is present in the periodontal pockets of more than 50% of adults with refractory periodontitis and 90% of patients with localized aggressive periodontitis (formerly called *localized juvenile periodontitis*), a destructive form of periodontitis characterized by loss of the alveolar bone of the molars and incisors. Clonal spread of the organism within families has been demonstrated using polymerase chain reaction (PCR)–based typing systems.[5]

A. actinomycetemcomitans is classified into seven serotypes (a through g). The prevalence of different serotypes and their association with

periodontal disease varies among geographic and ethnic populations. The JP2 strain of serotype b has enhanced virulence and is associated with significantly higher prevalence of periodontitis in people of African and Mediterranean descent. Serotype c is the most prevalent subgingival type in Asian individuals as well as in Brazil and the United States.[6] Serotypes a, b, and c are detected most frequently in German patients, and c and d are found in Korean patients.[7]

A. actinomycetemcomitans is a successful pathogen with well-characterized virulence factors, including two exotoxins: leukotoxin and cytolethal distending toxin (Cdt). The leukotoxin selectively binds to β_2-integrin and destroys leukocytes by inducing apoptosis or lysis.[8] Cdt is prevalent among certain gram-negative bacteria and acts by damaging DNA, which produces growth arrest and subsequent apoptosis of a wide variety of eukaryotic cell types.[8] Other virulence factors include proteins Aae and ApiA, which allow the organism to adhere to epithelial cells and become internalized. Production of didanosine tetraphosphate may enhance bacterial survival within the cytoplasm.[9] Induction of cytokines and other factors contribute to tissue destruction and resorption of alveolar bone.[10] Intracellular survival allows the organism to evade the host immune response, penetrate the epithelial cell layer, and reach the underlying connective tissues. *A. actinomycetemcomitans* is further able to evade host immune responses by inducing increased expression of Toll-like receptor 2, leading to phagocytosis and apoptosis of macrophages via p38 mitogen-activated protein kinase activation and tumor necrosis factor-α production.[11] *A. actinomycetemcomitans* in biofilms is strongly associated with loss of periodontal tissue attachment. The ability of this organism to adhere to abiotic surfaces and form biofilms has been attributed to type IVb–like fimbriae that are primarily composed of fimbrial lower-molecular-weight protein (Flp).

A. actinomycetemcomitans is one of the HACEK organisms, along with *Haemophilus parainfluenzae,* other *Aggregatibacter* spp. (*A. aphrophilus* [formerly *Haemophilus aphrophilus*] and *A. segnis*), *Cardiobacterium* spp. (*C. hominis, C. valvarum*), *Eikenella corrodens,* and *Kingella* spp. (*K. kingae, K. denitrificans*), which have in common that they are part of the normal oral microbiota, and have slow growth in culture, the need for incubation in an atmosphere enhanced with CO_2 for recovery in culture, and a predilection for causing endocarditis. The onset of endocarditis is usually insidious, with a mean time to diagnosis of about 3 months. In comprehensive reviews of *A. actinomycetemcomitans* endocarditis, almost half of patients had periodontal disease or recent dental work and over 60% had underlying native valvular disease (33%) or prosthetic valves (28%).[2,12] Fever was present in fewer than 50%; peripheral manifestations and splenomegaly each occurred in about one-third. Therapy was successful in 85% to 91%, but significant embolization was common (39%) and 23% required valve replacement.[2]

Prosthetic valve endocarditis with *A. actinomycetemcomitans* was usually recognized earlier than native valve endocarditis (42 vs. 106 days), which probably was attributable to a higher index of suspicion. This earlier diagnosis may account for the high cure rate achieved with antibiotics alone and a relatively low rate of embolization reported.

Culture isolation of *A. actinomycetemcomitans* is the usual means of diagnosis, and the fastidious, slow-growing nature of the organism makes this difficult. Cultures must be incubated in an enhanced (5%–10%) CO_2 atmosphere. By 18 to 24 hours, a few colonies (punctate, nonhemolytic) may be apparent on blood or chocolate agar, but the organism grows slowly and incubation for at least 48 hours is needed. After further incubation, a starlike structure tends to form in the center of the mature colony. The organism grows poorly on MacConkey agar. In broth or blood cultures, the organism often grows only in small "granules" adherent to the sides of the tube or bottle, with the medium remaining clear. Although the mean duration for incubation using continuously monitored blood cultures until detection is 3 to 5 days, up to 30 days may be required, especially if the patient has received prior antibiotic therapy.[12] This finding underscores the need to hold blood culture bottles for a prolonged time if endocarditis caused by a fastidious organism is suspected. The appearance of the organism on Gram stain is coccoid to coccobacillary, similar to *Haemophilus* species. *A. actinomycetemcomitans* is urease negative and indole negative, reduces nitrate, and usually is oxidase negative. It is catalase positive, which helps differentiate it from *A. aphrophilus*.[1] Most of the HACEK organisms are included in current MALDI-TOF mass spectrometry databases, which allows for rapid and more accurate identification.

A. actinomycetemcomitans usually is susceptible to cephalosporins (especially third-generation agents), rifampin, trimethoprim-sulfamethoxazole, aminoglycosides, fluoroquinolones (including ciprofloxacin and moxifloxacin), tetracycline, azithromycin, and chloramphenicol.[2,13] In vitro susceptibility to penicillin and ampicillin is variable, but test results do not necessarily correlate with the clinical outcome. In general, treatment of actinomycosis with penicillin and surgical drainage (when necessary) is sufficient, even when mixed infection is present. Vancomycin, erythromycin, and clindamycin have little activity against *A. actinomycetemcomitans.* The organism displays variable susceptibility to metronidazole, and in vitro synergy between metronidazole and both β-lactams and ciprofloxacin has been reported.[14] Because of strain-to-strain variability, testing of clinical isolates is recommended. CLSI provides conditions and breakpoints for broth microdilution susceptibility testing.[15] The bioMérieux Etest (bioMérieux, Inc., Hazelwood, MO) can be used with supplemented Mueller-Hinton agar, *Haemophilus* test medium, or *Brucella* agar supplemented with 5% sheep blood, hemin, and vitamin K incubated at 5% CO_2 for 24 to 72 hours. In the past, penicillin or ampicillin combined with an aminoglycoside was the usual treatment for endocarditis caused by this organism. Because of the potential for β-lactamase production, reports of failures with penicillin therapy, and difficulties with susceptibility testing, third-generation cephalosporins are now considered the drugs of choice. For endocarditis caused by HACEK organisms, the American Heart Association guidelines endorsed by the Infectious Diseases Society of America recommend ceftriaxone or ampicillin-sulbactam as initial therapy.[16] A fluoroquinolone may be used to treat patients with β-lactam allergy, but clinical data are limited.

A. actinomycetemcomitans endocarditis has developed after dental procedures despite the prophylactic use of penicillin, erythromycin, or vancomycin. Severe *A. actinomycetemcomitans*–associated periodontitis is usually treated with mechanical débridement in combination with oral tetracycline therapy. Tetracycline failures occur, however, and a report suggests that the combination of metronidazole and amoxicillin is effective in suppressing subgingival infection.[17]

Five species of *Actinobacillus*—*A. lignieresii, A. equuli, A. suis, A. hominis,* and *A. ureae*—are rare causes of human disease. The first three are commensals and opportunistic pathogens in animals, whereas the latter two are commensals of the human upper respiratory tract.[1] *A. lignieresii, A. suis,* and *A. equuli* rarely can cause infections after bite wounds from farm animals.[18] These infections can be polymicrobial. One report has described a boar hunter who developed endocarditis caused by an *Actinobacillus* organism that resembled *A. suis* and *A. hominis* biochemically.[19] Another report described 46 clinical *A. hominis* isolates acquired over a 22-year period, mostly from Copenhagen, Denmark.[18] Before this report, there were only a few case reports of human infections caused by this organism. Most of the isolates were from the respiratory tract; 18 of 33 respiratory isolates were reported to be pure cultures of *A. hominis.* The remaining respiratory cultures contained at least one other common respiratory pathogen. All the patients in this series had underlying diseases, including alcoholism, cardiovascular disease, drug addiction, chronic obstructive pulmonary disease, and cancer. Most patients had fever and pulmonary infiltrates, and 9 of 36 patients for whom clinical information was available died, including 1 of the 2 patients with bacteremia. The identification of the *A. hominis* isolates was confirmed by ribotyping and DNA hybridization. In this and other reports, automated systems had difficulty identifying *Actinobacillus* species. Fatal *A. hominis* bacteremia has also been reported in two patients with severe underlying liver disease.[20] *A. ureae* is a rare cause of bacteremia and meningitis. Nine of 14 cases of *A. ureae* meningitis were posttraumatic, and another occurred after neurosurgery.[21] Several patients had underlying chronic illnesses, including alcoholism and human immunodeficiency virus (HIV) infection.

Identification of *Actinobacillus* species is problematic. At the genus level, these organisms are biochemically similar to *Pasteurella* species. Species identification can be difficult without DNA hybridization studies.

A. ureae meningitis has been treated successfully with penicillin and third-generation cephalosporins.[21]

Aeromonas Species

Aeromonads are ubiquitous inhabitants of fresh and brackish water. They have also been recovered from chlorinated tap water, including hospital water supplies. They occasionally cause soft tissue infections and sepsis in immunocompromised hosts and increasingly have been associated with diarrheal disease and other infections in immunocompetent individuals.

Taxonomy of the aeromonads has been revised over the past few decades and continues to be in transition. Aeromonads are broadly divided into the mesophilic group, with optimal growth temperatures of 35°C to 37°C and associated with human infection, and the psychrophilic group, with optimal growth temperatures of 22°C to 25°C and associated with disease in fish. The species designations within the mesophilic group are currently largely based on DNA hybridization studies, but new information based on full-genome sequencing and microarray analysis will likely result in further taxonomic revisions.[22] *A. hydrophila, A. caviae* (synonym, *A. punctata*), and *A. veronii* biovar *sobria* are reported most frequently in human infections.[22] The pathogenic potential of *Aeromonas* species has been attributed to several virulence factors that are very heterogeneously present among clinical isolates. The pathogenicity of *A. hydrophila* has been attributed to the ability of the bacterium to produce the cytotoxic enterotoxin Act and cytotonic enterotoxins Ast and Alt, as well as a variety of proteases and type III secretion systems and surface structures, including pili and S-layer, lateral, and polar flagella, which allow the organism to attach to cells and enter tissue.[22] Carriage of multiple toxins appears to be a property of *A. hydrophila* but not other *Aeromonas* species. The aerolysin/hemolysin group of toxins, including Act, are important virulence factors in *A. caviae* and *A. veronii* biovar *sobria.* Alt and lateral flagella are notably significantly less prevalent in these species.[22]

Aeromonas was first isolated more than 70 years ago, but evidence implicating this genus as a cause of gastrointestinal disease has been amassed only since the early 1980s. Reports from diverse geographic locations have associated *Aeromonas* species with diarrheal disease in humans; in some locales, they are recovered as commonly as *Shigella* or *Campylobacter.* Many laboratories do not routinely culture stool for *Aeromonas,* so the incidence of *Aeromonas*-associated diarrhea may be underestimated. Evidence supporting a causative role in diarrheal disease includes (1) a higher carriage rate in symptomatic compared with asymptomatic individuals; (2) an absence of other enteric pathogens in most symptomatic patients harboring *Aeromonas* species; (3) identification of *Aeromonas* enterotoxins[22]; (4) improvement of diarrhea with antibiotics active against *Aeromonas* species and clinical worsening with antibiotics ineffective against the organism; and (5) evidence of a specific secretory immune response coincident with diarrheal disease.[23] Most of this information refers to *A. hydrophila* and *A. cavie*; the extent of clinical information about the other species in relation to diarrheal disease is limited.

Aeromonas caviae is the predominant isolate from diarrheal stools, but in some geographic areas, *A. hydrophila* and *A. veronii* biovar *sobria* are frequently isolated as well.[22,23] Other *Aeromonas* species appear to cause asymptomatic carriage only.[22] *Aeromonas*-associated diarrhea usually occurs during the summer, when the concentrations of aeromonads in water are the highest. Most cases are sporadic. An epidemiologic study was unable to implicate the drinking water supply as the source of diarrheal isolates; *Aeromonas* isolates from diarrheal stool were genetically unrelated to those from water supplies.[24] *Aeromonas* is increasingly being recognized as a cause of diarrhea in travelers returning from Asia, Africa, and Latin America.[22] Daycare center outbreaks have been reported, although in one study, molecular typing did not suggest clonal spread.[22] The clinical manifestations of *Aeromonas*-associated diarrhea are varied. Diarrhea is usually watery and self-limited, but some persons develop fever, abdominal pain, and bloody stools. Fecal leukocytes may be present. Occasionally, diarrhea may be severe or protracted, and hospitalization may be necessary. Rare cases of ischemic colitis associated with *Aeromonas* have been reported in healthy children and adults, and chronic colitis developing after acute *Aeromonas*-associated diarrhea has been reported in adults.[22,25] Although no controlled trials have validated antimicrobial therapy for *Aeromonas*-associated diarrhea, clinical improvement has occurred with antibiotics active against the organism. Hemolytic-uremic syndrome associated with *Aeromonas* enterocolitis has been described in infants and adults.[22] *Aeromonas*-associated diarrhea has been shown to be more prevalent in individuals with concurrent rotavirus infection. The relevance of this finding is supported by in vitro studies demonstrating that preinfection of enterocyte-like cells with rotovirus can increase the capacity of some *Aeromonas* strains to adhere to enterocytes.[26]

In contrast, the evidence for pathogenic roles of aeromonads in extraintestinal infections is much more clear-cut. Most *Aeromonas* soft tissue infections are caused by *A. hydrophila.* Trauma followed by exposure to fresh or brackish water (and not salt water, even though aeromonad density in seawater is similar to that in fresh water) usually, but not invariably, precedes infection.[22] Cellulitis develops within 8 to 48 hours, and systemic signs are common.[27] Suppuration and necrosis around the wound are frequent, and surgical débridement is often necessary. Fasciitis, myonecrosis (occasionally associated with gas formation), and osteomyelitis may develop. In the setting of a rapidly progressive cellulitis after an injury related to water exposure, *Aeromonas* and *Vibrio* species infections should be considered in the differential diagnosis. *Aeromonas* soft tissue infections can develop after exposure to soil, in association with crush injuries, and as a complication of burns, typically when initial management of the burn included immersion in natural water sources.[22] There is one reported outbreak of *A. hydrophila* wound infections in participants of a mud football competition in Australia. The field was "prepared" with water from an adjacent river but DNA fingerprints of the river isolates did not match those of the human isolates.[28] *Aeromonas* was second only to *Staphylococcus aureus* in one study of bacteria causing secondary infection in untreated Buruli ulcer lesions.[29] *Aeromonas* soft tissue infection is a recognized complication of the use of medicinal leeches in conjunction with reimplantation or flap surgery.[30] *A. hydrophila* and other *Aeromonas* species are normal inhabitants of the foregut of leeches. Leeches lack the requisite proteolytic enzymes and are dependent on the symbiotic *Aeromonas* to digest the blood meal. *Aeromonas* infection has developed in about 12% of patients treated with leeches.[28] Prophylactic antibiotics, particularly ciprofloxacin or cefotaxime, have been recommended at the time of leech application.[30,31] Infections have developed despite prophylaxis, with the isolated strains determined to be resistant to ciprofloxacin.[30,31] The onset of infection after the application of medicinal leeches ranges from 1 day to more than 10 days. Mild wound infection, loss of flap, myonecrosis, and sepsis may ensue.

Aeromonas bacteremia and sepsis are uncommon, but in the largest series reported to date, 143 *Aeromonas* bacteremias, including 104 that were monomicrobial, occurred in one institution in Taiwan over a 10-year period.[32] *A. hydrophila* caused 60% of the bacteremias; most of the other isolates that were identified by species were *A. veronii* subtype *sobria* and *A. caviae.*[32] Most patients in this series were immunocompromised, including 54% who were cirrhotic and 21% who had an underlying malignancy. Spontaneous bacterial peritonitis was common in cirrhotic patients with abdominal pain. There was a similar distribution of *Aeromonas* species in a study of 53 *Aeromonas* blood isolates collected from 27 medical centers in the United States over a 10-year period.[33] Most patients were immunocompromised, and underlying malignancy was much more common than liver disease in this series. Most patients with *Aeromonas* sepsis do not present with diarrhea. Interestingly, about one-third of *Aeromonas* bacteremias are hospital acquired.[34] *Aeromonas* has been recovered from hospital water supplies, and clusters of *Aeromonas* bacteremia have been described.[35] In some series, the hospital-onset cases were not epidemiologically linked and endogenous gut microbiota was the presumed source.[34] The mortality rate for *Aeromonas* sepsis is 33% or higher.[22] Other species—*Aeromonas jandaei, Aeromonas veronii* biovar *veronii,* and *Aeromonas schubertii*—have rarely been isolated from the blood.[22] A variety of other infections caused by *Aeromonas* species have been reported, including intraabdominal abscess, pancreatic abscess, hepatobiliary infection, spontaneous bacterial peritonitis in patients with cirrhosis, meningitis, endocarditis, suppurative thrombophlebitis, osteomyelitis, urinary tract infection, prostatitis, pneumonia (including near-drowning–associated pneumonia), empyema, lung abscess, tonsillitis, epiglottitis, keratitis, and otitis media.[22] *A. hydrophila* epididymitis and bacteremia developed in a healthy man 24

hours after he had sexual intercourse with his wife in their swimming pool. Cultures obtained from the pool grew *A. hydrophila.*[36]

Aeromonas organisms are gram-negative, nonsporulating facultative anaerobic rods that usually are β-hemolytic on blood agar and ferment carbohydrates with acid and gas production. The organisms grow well on MacConkey agar (some strains are lactose fermenters and some are not), but growth on thiosulfate citrate–bile salts–sucrose medium is variable. Selective techniques are often necessary for the isolation of *Aeromonas* species from mixed cultures. The organisms are more difficult to identify in stool cultures because enteric media may be inhibitory for some *Aeromonas* species. Either blood agar that contains ampicillin (10 or 30 μg/mL) or cefsulodin irgasan novobiocin agar can be used as a selective medium.[22] Growth of colonies on plates usually occurs within 24 hours. *Aeromonas* species are oxidase positive, helping to distinguish these organisms from Enterobacteriaceae. Identification of *Aeromonas* to the genus level is generally not difficult, but misidentifications, particularly as *Vibrio* species, may occur with automated systems.[22] Identification to species can be difficult and many clinical laboratories proceed no further, reporting an *Aeromonas* isolate as "*Aeromonas* species" or "*Aeromonas hydrophila* complex." MALDI-TOF mass spectrometry can provide rapid and accurate identification. CLSI document M45-A2 provides interpretive criteria for disk diffusion and MIC testing for several species of *Aeromonas.*[15] The clinically relevant *Aeromonas* species are uniformly resistant to penicillin and ampicillin, are often resistant to cefazolin and ticarcillin, and are usually but not invariably susceptible to third-generation cephalosporins, aztreonam, and carbapenems.[22] Resistance to cefotaxime has developed on therapy.[32] Sensitivity to piperacillin and ticarcillin-clavulanate is variable. *Aeromonas* species can produce serine β-lactamases, including an Ambler class D penicillinase, class C cephalosporinase, and, less frequently, Temoniera (TEM) family extended-spectrum β-lactamases.[22] Some isolates exhibit coordinated expression of these β-lactamases after both induction and selection of derepressed mutants.[22] *Aeromonas* can also harbor chromosomal CphA metallo-β-lactamases that have narrow substrate profiles and specifically hydrolyze carbapenems.[22] Metallo-β-lactamases of the Verona integron–encoded (VIM) and imipenemase (IMP) families that confer broader β-lactam resistance have been described in strains of *A. hydrophila* and *A. caviae,* encoded on an integron and a plasmid, respectively.[22] There are reports of increasing resistance to tetracycline and trimethoprim-sulfamethoxazole. In one report, tigecycline was active against 200 of 201 isolates.[37] Aminoglycosides are usually active, with resistance to tobramycin being more common than resistance to gentamicin or amikacin.[38] Fluoroquinolones are highly active against *Aeromonas* species, although the existence of chromosomal mutations and plasmid-mediated quinolone resistance in environmental *Aeromonas* strains raise concern that fluoroquinolone resistance could easily develop.[39] *Aeromonas* species harboring a conjugative plasmid that confers multiple antibiotic resistance have been identified.[40] A cephalosporin or fluoroquinolone is generally recommended for treatment of *Aeromonas,* with the addition of an aminoglycoside for severe infections.[38,39] Because of emerging resistance, polymicrobial therapy may be considered for empirical treatment until in vitro susceptibility results are available.

Cardiobacterium Species

Cardiobacterium hominis and *Cardiobacterium valvarum* are the only two species in the genus *Cardiobacterium.* Unlike the other HACEK organisms, these organisms rarely cause disease other than endocarditis. *Cardiobacterium* species have been described as *Pasteurella*-like organisms; they are part of the microbiota in the nose, mouth, and throat and are present occasionally on other mucous membranes as well as in the gastrointestinal tract.

There are more than 80 reported cases of *C. hominis* infection, and all but a few have involved the heart valves. Most patients have had underlying anatomic defects (e.g., rheumatic heart disease, ventricular septal defect, congenital bicuspid valve) or prosthetic cardiac valves.[41,42] Many patients with endocarditis have had severe periodontitis or prior dental procedures without antimicrobial prophylaxis. *C. hominis* endocarditis occurring after upper gastrointestinal endoscopy has been reported.[43] A subacute presentation, with an insidious onset (mean of 2–5 months before diagnosis) and an absence of fever at the time of diagnosis, is common.[44] Some of the patients have splenomegaly, anemia, immune-mediated glomerulonephritis, and hematuria, consistent with a long period between infection and diagnosis. Large vegetations, and large vessel emboli, are characteristic. The mortality rate is about 10%, and valve replacement is needed in about 30% of cases.[12] Septic arthritis, vertebral osteomyelitis, mycotic aneurysms (intracranial and mesenteric), and neurologic involvement are reported complications of *C. hominis* endocarditis.[44]

Almost all clinical isolates come from blood, although meningitis associated with endocarditis has been described. In one of the very rare cases of infection without endocarditis, a patient with adenocarcinoma of the kidney invading the cecum developed an abdominal abscess and bacteremia; abscess and blood cultures grew *C. hominis* and *Clostridium bifermentans.*[45] There is also a case report of *C. hominis* pacemaker lead infection without valvular involvement.[46] Because of phenotypic similarities, it is suspected that some clinical isolates identified as *C. hominis* may actually have been *C. valvarum. C. valvarum* has caused several endocarditis cases worldwide with a spectrum of presentations similar to *C. hominis,* including insidious infection, ability to cause embolism, and the need for valve replacement in the majority of cases.[47] Most cases for which details were provided were associated with periodontitis or an antecedent dental procedure without antimicrobial prophylaxis.[47] This species was first described as *Cardiobacterium* species strain B from dental plaque and has also been described among the etiologic agents in advanced lesions of children with noma.[48]

Cardiobacterium species are pleomorphic gram-negative rods; morphology varies considerably depending on culture conditions. They often have swelling of one or both ends and retain the crystal violet dye at the poles during the Gram stain procedure. Microscopically, the organisms sometimes form rosettes, but short chains, teardrops, pairs, and clusters are also common. Supplementation of the medium with yeast extract results in a loss of the pleomorphism, and most organisms become sticklike, gram-negative rods with rounded ends. Incubation in high humidity and 3% to 5% CO_2 maximizes recovery of the organism. Most strains grow better on sheep blood agar than chocolate agar and will grow on Mueller-Hinton agar or trypticase soy agar without blood, but grow poorly on MacConkey agar or similar selective media. Colonies of *C. hominis* are 1 to 2 mm in diameter on sheep blood agar, usually by 48 to 72 hours after incubation at 37°C under increased CO_2. However, with some systems, incubation for 5 to 7 days before growth can be confirmed is not unusual, and cultures should be held for this period or longer if *C. hominis* is suspected. *C. valvarum* is considered to be more fastidious than *C. hominis,* with tiny visible colonies, 0.2 to 0.8 mm in diameter, appearing on blood agar after 72 to 96 hours of incubation. Colonies of *C. valvarum* are nonhemolytic; however, colonies of *C. hominis* produce slight α-hemolysis after 3 to 4 days of incubation and develop a rough appearance, with a serpentine pattern of growth from the edge to adjacent colonies.[49] *Cardiobacterium* organisms are oxidase positive and catalase negative, and they produce indole (although positivity is weak in many strains of *C. hominis* and absent in some oral strains of *C. valvarum*). *Cardiobacterium* species may be misidentified as *Pasteurella multocida* when using the API 20NE identification strip (bioMérieux, Inc., Hazelwood, MO).[49] The phenylphosphonate reaction can be used to separate *C. hominis* (positive) from *C. valvarum* (negative).[47] MALDI-TOF mass spectrometry also successfully identifies *Cardiobacterium* and distinguishes the two species.[50] PCR amplification of 16S ribosomal DNA from heart valve and arterioembolic tissue has detected *C. hominis* sequences in cases of culture-negative endocarditis.

Susceptibility tests are difficult to perform because of the slow growth of the organism and unusual nutritional requirements, although the Etest appears to be useful.[49,51] When tested, the organism is usually broadly susceptible to β-lactam drugs, fluoroquinolones, chloramphenicol, rifampin, and tetracycline.[51] Susceptibility to aminoglycosides, erythromycin, and clindamycin is variable. Isolates with the ability to produce β-lactamase have been reported.[44] Current American Heart Association guidelines recommend treating endocarditis caused by HACEK organisms with a 4-week course of ceftriaxone, ampicillin-sulbactam, or a fluoroquinolone.[16] In a review of cases, most patients

were treated successfully with penicillin alone, ceftriaxone alone, or penicillin and aminoglycosides, with the duration of therapy ranging from 25 to 63 days.[47] Although microbiologic cure is usually achieved, complications frequently arise during the course of therapy. Systemic embolization, mycotic aneurysm, or progressive cardiac failure has necessitated valve replacement in a number of cases.

Chromobacterium Species

Chromobacterium violaceum is a rare opportunistic human pathogen but can cause life-threatening sepsis with metastatic abscesses. The organism is a common soil and water inhabitant in tropical and subtropical areas. Most cases of human infection have come from Southeast Asia, although more than 35 cases have been reported in the United States, almost all from the Southeast (primarily Florida). Cases have also been reported from Australia and South America. Although not considered a normal inhabitant of the human gastrointestinal tract, *C. violaceum* was present in the feces of 3 of 65 children whose stool was cultured at the time of admission to a hospital in Atlanta.[52]

C. violaceum infection occurs in infants, children, and adults, almost always in the summer months and usually after exposure of nonintact skin to contaminated water (often stagnant) or soil. Two cases followed near drownings. Symptoms include pain at a local site of infection, fever, nausea, vomiting, abdominal pain, and diarrhea. Local cellulitis, pustules, ulcers with necrotic bases, or lymphadenitis commonly precedes evidence of systemic infection. Septic shock develops rapidly, as can pneumonia and visceral abscesses involving the liver, spleen, and lungs. This presentation can be confused with septicemic melioidosis, which is more common than *C. violaceum* infection in Southeast Asia, where both diseases are endemic. The mortality rate for reported cases in the United States is about 60%. Urinary tract infection, conjunctivitis, orbital cellulitis, retropharyngeal infection with prevertebral abscess, neutropenic sepsis, osteomyelitis, brain abscess, meningitis, puerperal sepsis, and internal jugular vein thrombophlebitis have been reported. There are also a few case reports in the pediatric literature of *C. violaceum*–associated diarrhea. A report from Brazil of one confirmed and two suspected cases in siblings is the first cluster of suspected *C. violaceum* infections linked to a common source.[53] *C. violaceum* infection is more common in patients with chronic granulomatous disease (CGD), but cases occur in the apparently normal host.[54] There appears to be a higher survival rate in persons with CGD compared with patients without known neutrophil dysfunction. This may reflect a selection bias because *C. violaceum* infection can be the initial manifestation of CGD, with the diagnosis of CGD being established only after recovery from the infection. Deficiency of polymorphonuclear leukocyte glucose-6-phosphate dehydrogenase and neutrophil dysfunction also were present in a 3-year-old patient who died with *C. violaceum* sepsis. Most strains produce an antioxidant pigment, violacein, that protects the organism against oxidative stress induced by the host response to infection. Other pertinent virulence factors based on the study of only one clinical and one environmental isolate include greater endotoxicity of the outer membrane and enhanced resistance to phagocytosis in the virulent strain.[55] Diagnosis is made by culture of blood, abscess fluid, or skin exudate.

C. violaceum organisms are long gram-negative bacilli; occasionally, the organisms are slightly curved and can be confused with vibrios. The organisms are facultatively anaerobic, with versatile and adaptable pathways for energy generation, and grow readily in 18 to 24 hours on common laboratory media containing tryptophan, which include sheep blood agar, chocolate agar, Mueller-Hinton agar, trypticase soy broth, and MacConkey agar. Incubation at 37°C usually is effective, although growth is enhanced if incubation occurs at 25°C. Most strains produce violacein, an insoluble pigment that imparts a violet-black color to the colonies on solid media under aerobic conditions, hence the species' name (Fig. 236.1). There are a few reports of infection caused by nonpigmented strains. Violacein can induce apoptosis in leukemia cell lines and is being investigated as a potential chemotherapeutic agent.[56] The color may be lost on subculture or after therapy is begun. The organisms produce hydrogen cyanide, so a faint cyanide smell may be present. The oxidase reaction is usually positive but may be difficult to detect in pigmented strains. Demonstration of oxidase can be enhanced by incubating the culture anaerobically, which inhibits pigment formation.[53]

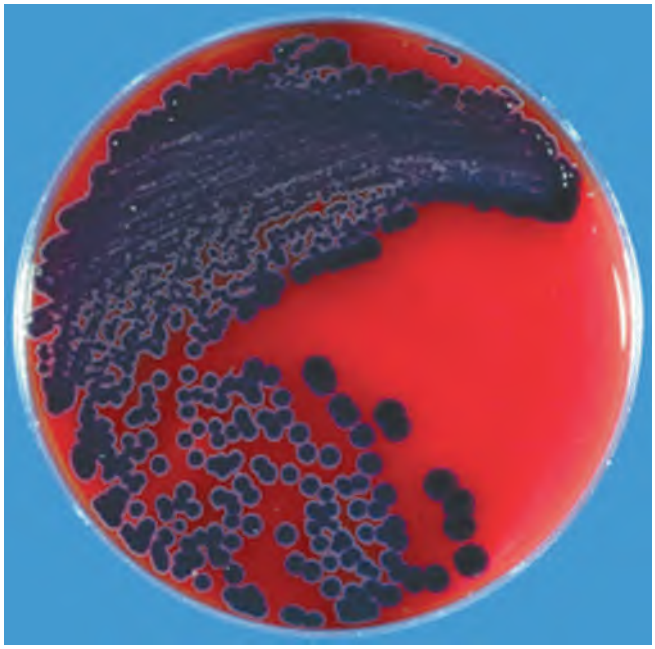

FIG. 236.1 Violet-black colonies of *Chromobacterium violaceum* from production of the pigment violacein.

Antibiotics having the greatest activity against *C. violaceum* generally include fluoroquinolones, chloramphenicol, tetracycline, trimethoprim-sulfamethoxazole, imipenem, and gentamicin.[57] The ureidopenicillins are often active, but resistance to cephalosporins is common. *C. violaceum* is also resistant to colistin. Although aztreonam is a natural product of some strains of *C. violaceum,* most clinical isolates are susceptible to this agent.[58] Because of the rarity of infection, the often fulminant course, and the high mortality rate, the optimal antibiotic therapy is unknown. Ciprofloxacin is the most active antibiotic in vitro, and there are recent case reports of successful treatment with fluoroquinolones, often in combination with other agents. Most survivors of this infection were treated with chloramphenicol or a penicillin (carboxypenicillin or a ureidopenicillin) in combination with an aminoglycoside. Relapse has occurred more than 2 weeks after the completion of therapy and apparent cure, presumably because of a residual suppurative focus.[53] Oral trimethoprim-sulfamethoxazole, doxycycline, or ciprofloxacin has been used after 2 to 4 weeks of intravenous therapy with other antibiotics, with the oral regimen continued for several weeks to a few months to prevent relapse. Antibiotics at subinhibitory concentrations, such as occur during the postantibiotic phases of clinical therapy, have been shown to enhance quorum-sensing–related virulence factors, including violacein production, chitinase production, and biofilm formation.[59]

Chromobacterium haemolyticum, a species newly described in 2008, has been reported to cause pediatric bacteremia, proctocolitis in children, pneumonia, and necrotizing fasciitis.[60–62] These cases have been reported from the United States, Japan, and Thailand. There was known aquatic exposure in two of the cases. *C. haemolyticum* differs from *C. violaceum* in that it is nonpigmented and has strong β-hemolytic activity on sheep blood agar. Although there are also differences in several biochemical reactions, misidentifications of *C. haemolyticum* as nonpigmented *C. violaceum* occur with currently available biochemical and MALDI-TOF mass spectrometry systems; 16S rRNA sequencing is required for definitive identification. Overall, *C. haemolyticum* is more resistant than *C. violaceum,* with higher MICs for most drugs. Isolates are typically susceptible to fluoroquinolones and resistant to β-lactam antibiotics.

Dysgonomonas Species

The genus *Dysgonomonas* taxonomically clusters in the *Bacteroides-Prevotella-Porphyromonas* group and presently contains four species—*D.*

gadei, D. capnocytophagoides, D. mossii, and *D. hofstadii*—that have been isolated from human sources. The type species is *D. gadei* but *D. capnocytophagoides* has been reported more frequently. *D. capnocytophagoides* and *D. mossii* were originally members of the Centers for Disease Control and Prevention (CDC) dysgonic fermenter (DF)-3 group, indicating an organism that ferments glucose and has difficulty growing on routine media. Isolates from the genus *Dysgonomonas* are rare but have been recovered from blood, wounds, urine, peritoneal fluid, umbilicus, stools, and gallbladder.

D. capnocytophagoides has been isolated from diarrheal stools of patients with immune deficiencies, including common variable hypogammaglobulinemia, HIV infection, diabetes with chronic renal failure, and lymphoreticular and other malignancies, and from patients receiving immunosuppressive agents, but its role as a gastrointestinal pathogen remains controversial.[63,64] With the use of selective media, this organism was isolated from 11 of 690 (1.6%) stools submitted for bacterial culture at the National Cancer Institute.[64] In another prospective study of the role of *D. capnocytophagoides* in diarrheal disease, the organism was recovered from 2 of 178 specimens (1.1%) submitted for *Clostridioides difficile* (formerly *Clostridium difficile*) toxin assay and from 3 of 129 (2.3%) stool specimens from patients with HIV infection. These data suggest that the paucity of reports of recovering *D. capnocytophagoides* from stool specimens may not be attributable to its rarity (as a colonizer or pathogen) but rather to the inability to recover the organism on conventional media. Antibiotic therapy directed at *D. capnocytophagoides* produced a therapeutic response in some of these patients, including 4 of 11 in the first study. Some of the responders had diarrhea of several months' duration, with prompt resolution after antibiotic therapy was initiated. In other patients, the clinical significance of the organism was unclear; eradication of the organism from the stool was not accompanied by resolution of diarrhea, or the diarrhea resolved without specific therapy. *D. capnocytophagoides* has also been isolated from the urine as a cause of biliary sepsis,[65] from a polymicrobial thigh abscess in a patient with insulin-dependent diabetes,[66] from liver abscesses and blood after radiofrequency ablation in a patient with hepatocellular carcinoma,[67] and from patients with neutropenia, including the blood and stool of a patient with acute myelocytic leukemia.[68] *D. gadei* and *D. mossii* have been isolated from the gallbladders of patients with cholecystitis.[69] *D. mossii* has also been recovered repeatedly from intestinal fluid in a patient with pancreatic cancer but was not associated with obvious infection.[69] *D. hofstadii* was isolated from a postoperative abdominal wound.[70]

Organisms in the genus *Dysgonomonas* are coccobacillary to short gram-negative, nonmotile, facultative rods. Growth occurs on blood agar and chocolate agar after 1 to 3 days of incubation in ambient, CO_2-enriched, or anaerobic atmospheres, but growth is less on blood agar and no growth occurs on MacConkey agar. Routine enteric media do not support growth of *D. capnocytophagoides.* Selective *Campylobacter* media do support growth when incubated at 37°C, but not at 42°C, which is the routine incubation temperature for *Campylobacter.* Selective media such as cefoperazone vancomycin amphotericin B blood agar inhibit normal microbiota and allow recovery of *D. capnocytophagoides* from stool specimens.

Dysgonomonas colonies are gray-white and nonhemolytic with a slight sweet aromatic odor. X factor is required for growth, nitrate is not reduced, and oxidase and catalase tests are negative. Identification can be made using the API Rapid ID 32A system (bioMérieux, Durham, NC) or the VITEK 2 system (bioMérieux, Durham, NC) or by whole-cell fatty acid gas chromatography.[66,70]

Despite a lack of established breakpoints, the Kirby-Bauer disk diffusion and MIC methods have been used for antimicrobial susceptibility testing.[69,71] *Dysgonomonas* species appear to be resistant to most β-lactam drugs, fluoroquinolones, aminoglycosides, metronidazole, vancomycin, erythromycin, and gentamicin. Many strains are susceptible to chloramphenicol, trimethoprim-sulfamethoxazole, clindamycin, and tetracycline. Tetracycline or clindamycin was used in the few reported cases of diarrheal disease that responded promptly to antibiotic administration. Despite a Kirby-Bauer zone size suggesting susceptibility, imipenem failed to clear *D. capnocytophagoides* from the bloodstream in the one reported bacteremic patient; the bacteremia resolved after therapy with trimethoprim-sulfamethoxazole was initiated.

Kingella Species

Kingella species are members of the family Neisseriaceae. They are normal microbiota of the human oropharynx and also are occasionally found in the oral cavity in other animals. Five species—*K. kingae, K. denitrificans, K. oralis, K. potus,* and *K. negevensis*—have been described. *Kingella kingae* is the most frequently recognized member of the genus and has been isolated from invasive infections with the oropharynx implicated as the source. *Kingella kingae* is the most common cause of bone and joint infections in young children and belongs to the HACEK group of fastidious gram-negative organisms associated with endocarditis (see Chapter 213).

Kingella denitrificans has been implicated in cases of endocarditis, bacteremia, empyema, corneal ulcers, chorioamnionitis, granulomatous disease secondary to acquired immunodeficiency syndrome (AIDS), retropharyngeal abscess, and peritonitis in peritoneal dialysis patients.[72,73] The one reported pediatric peritonitis case was polymicrobial and the source of the organisms was presumed to be the patient's dog.[74]

The other *Kingella* species have been reported much less frequently. *K. oralis* has been isolated from subgingival plaque in patients with and without periodontitis, and its relationship to disease is unclear.[75] The only reported infection attributed to *K. potus* was in a forearm wound in a zookeeper as a result of a kinkajou bite.[76] *K. negevensis* is described as one of the oropharyngeal microbiota of healthy children but has not been studied in other populations.[77] In the only reported case of invasive infection to date, PCR targeting the GroEL molecular chaperone protein gene identified *K. negevensis* in a culture-negative osteoarticular specimen from a child.[78]

Kingella spp. are coccoid to medium-sized gram-negative rods that tend to resist decolorization and do not grow on MacConkey agar. The organisms are notoriously fastidious, and growth is enhanced in the presence of 5% to 10% CO_2. *K. denitrificans, K. potus,* and *K. oralis* colonies are low, convex, and 1 to 2 mm in diameter after 48 hours of incubation. They are friable and nonhemolytic and have a nondiffusible yellow pigment. *K. negevensis* colonies are said to resemble a small colony variant of *K. kingae* and are opaque, pinpoint, and faintly β-hemolytic. All species are catalase negative and oxidase positive. All species except *K. potus* ferment glucose. Automated biochemical identification systems can misidentify *Kingella* as *Haemophilus* spp., *Gardnerella vaginalis, Neisseria* spp., or *Moraxella* spp.[79] Current MALDI-TOF mass spectrometry databases include *K. kingae* and *K. denitrificans,* and these organisms have been correctly identified using this technology in several reports. Amplification and sequencing of the 16S rRNA gene or species-specific nucleic acid amplification tests targeting either the *rtx* operon or the *groEL* gene have been useful for detection of *Kingella* in some bone and joint specimens in which cultures have not revealed the pathogen.[80]

Approved breakpoints for broth microdilution susceptibility testing of the HACEK group have been published by the CLSI.[81] *Kingella* spp. are generally susceptible to a wide range of antibiotics, including β-lactams, macrolides, tetracyclines, co-trimoxazole, and quinolones. β-Lactamase–positive isolates have been reported to be susceptible to combinations with β-lactam inhibitors.

Neisseria animaloris and *Neisseria zoodegmatis*

The bacteria previously known as CDC eugonic fermenter (EF)-4 have been renamed *Neisseria animaloris* and *Neisseria zoodegmatis* based on polyphasic taxonomic studies, including 16S rRNA gene sequence analysis[82] These bacteria are nonmotile, oxidase-positive, fastidious gram-negative rods that produce acid from glucose (*eugonic fermenter*) but have relatively few other reactions and display very slow growth in anaerobic conditions. They are distinguished from *Cardiobacterium* and *Kingella* by the capacity to produce catalase and lack of indole production. Two biotypes were recognized based on the presence (EF-4a) or absence (EF-4b) of arginine hydrolase activity, DNA guanine-cytosine content, cellular fatty acid analysis, and whole-cell protein analysis. Organisms previously recognized as EF-4a are now *Neisseria animaloris* and EF-4b organisms are *Neisseria zoodegmatis.* These bacteria are normal inhabitants of the oral cavity of dogs and cats. Most human infections occur after dog bites, although infections associated with cat

bites or scratches occur as well.[83] The organism can be isolated from bite wounds that do not demonstrate signs of inflammation, but cellulitis, abscess formation, and fever may develop. Systemic infection or infection not involving skin or skin structures is extremely rare. Endophthalmitis caused by *Pasteurella multocida* and EF-4 occurred after a cat scratch in an 8-year-old girl.[84] There is one report of bloodstream infection occurring in a patient with hepatic carcinoid who denied being bitten by a dog or cat.[85] An otherwise healthy man whose dogs often licked him in the ears developed chronic EF-4 otitis media that required mastoidectomy.[86]

These bacteria usually appear as short rods on Gram stain but can also appear as small coccoid forms or long chains. The organisms grow well on blood agar and chocolate agar within 24 hours, but grow poorly or not at all on MacConkey and similar agars. Incubation in 5% CO_2 does not noticeably enhance growth. The colonies are small, may be slightly yellow-orange, and are smooth; some strains have a popcorn-like odor.

Penicillin G and ampicillin are active against these *Neisseria* species at concentrations attainable with oral administration, so amoxicillin-clavulanate, which is recommended for bite wounds, is adequate for coverage.[87,88] Fluoroquinolones and tetracycline can also be used as oral therapy. Chloramphenicol and aminoglycosides have activity, whereas cephalosporins, particularly first-generation agents, are less active in vitro.[87,88]

Plesiomonas shigelloides

Plesiomonas shigelloides, a ubiquitous freshwater inhabitant, has been implicated as a cause of acute diarrhea and, rarely, serious extraintestinal disease.[89] The name *Plesiomonas,* from the Greek word for "neighbor," was chosen because the organism was believed to be closely related to *Aeromonas.* Its classification has been a matter of some debate; it was previously classified in the family Vibrionaceae but is currently classified in the Enterobacteriaceae.[90] *P. shigelloides* is the only species in the genus. The organism was originally isolated in 1947 and given the name C27. It has also been named *Pseudomonas shigelloides, Aeromonas shigelloides,* and *Fergusonia shigelloides.*

P. shigelloides is a water- and soil-associated organism that replicates at temperatures above 8°C. It is found primarily in freshwater or estuary environments within temperate and tropical climates but can exist in seawater during the warm-weather months. Asymptomatic carriage of *P. shigelloides* is very rare among healthy persons. The usual vehicles of transmission of plesiomonads to humans are water; food such as oysters, shrimp, or chicken[89]; and a variety of animals that may be colonized with the organism.[91] The organism has been acquired during foreign travel. *P. shigelloides* is associated with gastroenteritis and has been identified as a cause of outbreaks, but the failure to identify an enteropathogenic mechanism, the lack of an animal model, and unsuccessful attempts to induce disease in volunteers make it impossible to firmly establish a causal relationship. Thus the clinical significance of finding the organism in a diarrheal stool is uncertain. An epidemiologic study in Ecuador found stronger evidence that *Plesiomonas* diarrhea was associated with rotavirus coinfection than single infection.[92] Potential virulence factors include β-hemolysins, cytotoxins, exoenzymes, and adherence factors, but their significance is unknown.[93]

The clinical presentation of individuals in whom *P. shigelloides* is isolated from diarrheal stool in the absence of detection of other pathogens varies from a mild self-limited illness to mucoid, bloody diarrhea with fecal leukocytes. A predominance of a secretory-type diarrhea has been noted,[89] but other series have found a high percentage with a clinical illness compatible with enteroinvasive disease featuring abdominal pain, fever, bloody diarrhea, and fecal leukocytes.[94] Most symptomatic patients have either traveled abroad or been exposed to potentially contaminated water or food. Outbreaks have been reported, particularly from Japan. The role of antibiotics for *Plesiomonas*-associated diarrhea is uncertain. Antimicrobial therapy did not shorten the duration of fever or diarrhea in Thai children with *Plesiomonas*-associated diarrhea.[95] On the other hand, in a small nonrandomized Canadian study of patients who developed *Plesiomonas*-associated diarrhea after travel abroad, 8 of 9 treated patients were asymptomatic within 2 weeks, compared with 6 of 15 controls ($P < .05$).[94]

Most descriptions of extraintestinal disease come from individual case reports. These reports include cases of osteomyelitis, septic arthritis, endophthalmitis, spontaneous bacterial peritonitis, pancreatic abscess, splenic abscess, biliary disease,[96] cholecystitis, cellulitis, pyosalpinx,[97] epididymo-orchitis, and pneumonia.[98] About 10 cases of neonatal sepsis with meningitis have been described.[99] Bacteremia is rare and usually occurs in immunocompromised hosts. In a case series of *Plesiomonas* bacteremia from Hong Kong, all seven patients were elderly; four had biliary tract disease, and three had underlying malignancy.[100] Bacteremia accompanying gastroenteritis has been reported in a healthy 15-year-old girl.

P. shigelloides is a motile, facultatively anaerobic, gram-negative, oxidase-positive bacillus. It is readily isolated from some enteric agars such as MacConkey agar but does not grow well on thiosulfate citrate bile salts sucrose medium. Selective techniques may be necessary for isolation of the organism from mixed cultures, such as the use of bile peptone broth or trypticase soy broth with ampicillin.[101] The organism grows well at 35°C and produces visible colonies (nonhemolytic) within 24 hours. The organism can now be identified on gastrointestinal multiplex molecular panels, but its clinical significance is uncertain.[102]

P. shigelloides is usually susceptible to chloramphenicol, trimethoprim-sulfamethoxazole, quinolones, cephalosporins, and imipenem.[95,103] Because of β-lactamase production, most isolates are now resistant to penicillins, including ureidopenicillins, although the β-lactamase inhibitor combinations appear to be active. Susceptibilities to aminoglycosides and tetracycline are variable. Antimicrobial therapy for established enteric infections is the same as for *Shigella* and generally includes a fluoroquinolone or azithromycin.[95] Systemic infections have been successfully treated with fluoroquinolones, carbapenems, or β-lactam/inhibitor combinations such as piperacillin-tazobactam.[97–100]

GLUCOSE NONFERMENTERS OR WEAK FERMENTERS

Achromobacter and *Alcaligenes* Species

The taxonomic designations for *Achromobacter* and *Alcaligenes* species have been particularly confusing. *Achromobacter xylosoxidans* was renamed *Alcaligenes xylosoxidans* subsp. *xylosoxydans,* but 16S rRNA sequence analysis and guanine-cytosine content studies support placement of this organism back in the genus *Achromobacter.*[104] Other *Alcaligenes* species—*A. ruhlandii, A. piechaudii,* and *A. denitrificans*—have also been transferred to *Achromobacter.* Organisms formerly considered *Achromobacter* groups A, C, and D (and before that, CDC groups Vd-1 and Vd-2) are now named *Ochrobactrum anthropi* and are considered separately (see "*Ochrobactrum* Species" later). *Achromobacter* species are nonfermenting gram-negative bacilli found in soil and water, including swimming pools, well water, municipal and hospital water supplies, dialysis solutions, ultrasound gel, and chlorhexidine solutions. They can occasionally be recovered from the respiratory and gastrointestinal tracts, primarily in persons with health care contact. Infection results when organisms are introduced into wounds or colonize those with compromised host defenses. Clinically relevant species include the asaccharolytic species *A. dentrificans, A. piechaudii,* and *Alcaligenes faecalis* (this organism remains in the genus *Alcaligenes*); the saccharolytic species *A. xylosoxidans*; and the unnamed *Achromobacter* group F. Although sometimes considered a contaminant, *Achromobacter* group B (now classified along with *Achromobacter* group E as *Pannonibacter phragmitetus*) has been recovered from the blood of patients with clinical sepsis and endocarditis.[105]

A. xylosoxidans is the most clinically important of these organisms. It probably is part of the endogenous microbiota of the ear and gastrointestinal tract and is a common contaminant of fluids.[106] The organism has been implicated in outbreaks of nosocomial infection associated with contaminated solutions (e.g., intravenous fluids, hemodialysis fluid, irrigation fluids, mouthwash), pressure transducers, incubators and humidifiers, and contaminated soaps and disinfectants.[107] Contamination of well water was the apparent source of bacteremia in one case. Clinical illness that is caused by *A. xylosoxidans* has involved isolates from blood, peritoneal and pleural fluids, urine, respiratory secretions, and wound exudates. Bacteremia, often related to intravascular

catheters, is the most commonly reported infection and is frequently polymicrobial in patients with underlying malignancies.[108,109] Biliary tract sepsis, meningitis (sometimes with lymphocytic predominance in cerebrospinal fluid), pneumonia (nosocomial and community acquired), peritonitis (including spontaneous bacterial peritonitis and peritonitis in patients on continuous ambulatory peritoneal dialysis), urinary tract infection, conjunctivitis, osteomyelitis, prosthetic knee infection, mesh infection, infected necrotizing pancreatitis, and prosthetic valve endocarditis have been reported.[106–114] Patients often have an immunosuppressed state such as cancer or HIV infection, but this is not always the case, especially in nosocomial outbreaks.[109,113] *A. xylosoxidans* as well as other *Achromobacter* species have been recovered with increasing frequency from respiratory secretions of persons with cystic fibrosis.[114] Colonization has been associated with exacerbation of respiratory symptoms, possibly as a result of exacerbation of the inflammatory response caused by lipopolysaccharide and a cytotoxic factor produced by *Achromobacter.*[114,115] Several case-control studies have not shown more rapid deterioration in clinical or pulmonary function status among cystic fibrosis patients chronically colonized with *Achromobacter* or *Alcaligenes* species, except in a subgroup of patients with a rapid increase in specific precipitating antibodies to *A. xylosoxidans.*[116] Recovery of *A. xylosoxidans* in neonatal infection may result from perinatal transfer from the mother.

A. denitrificans has been recovered as a single pathogen from blood, cerebrospinal fluid, and other normally sterile body fluids, as well as from a renal abscess and in mixed culture from sites usually containing normal microbiota.[117] Few recent publications have addressed the pathogenic role of these organisms. *A. piechaudii* was believed to cause chronic otitis in a diabetic patient[118] and has also been recovered from blood in a patient with a hematologic malignancy and an infected Hickman catheter who had recurrent bacteremia.[119]

Alcaligenes faecalis can be recovered in a variety of clinical settings. Most isolates of *A. faecalis* from blood or respiratory secretions are related to the contamination of hospital equipment or fluids with the organism, with resulting human colonization or infection. The urine is the other common site of recovery, although *A. faecalis* infrequently causes symptomatic urinary tract infection. It also has been recovered from corneal ulcers, ear discharges, wound drainage, peritoneal fluid, and feces.[120,121] It is rarely recovered in pure culture from any of these sites.

Phylogenetically and biochemically, *Alcaligenes* and *Achromobacter* are closely related to the genus *Bordetella. Achromobacter* species grow well on standard microbiologic media, including MacConkey agar. They produce flat, spreading, and rough colonies and have peritrichous flagella, features that help distinguish them from pseudomonads. The majority of strains will also grow on *Burkholderia cepacia* selective agar. The organisms are oxidase positive and catalase positive and oxidize glucose to produce acid, but are urease negative and indole negative. *A. xylosoxidans,* as the species name indicates, oxidizes xylose readily, which distinguishes it from other species in the genus. Distinguishing the organisms and confirming the identification is made difficult by their lack of reactivity in many biochemical or assimilation tests. MALDI-TOF mass spectrometry offers accurate identification of this group of organisms and will play an increasing role as the technology becomes more widely utilized.

An isolate of *A. xylosoxidans* can easily be mistaken for a non–*P. aeruginosa* strain of *Pseudomonas* or for a strain of the *B. cepacia* complex, but the unusual susceptibility pattern suggests the correct identity. Methods for susceptibility testing are not standardized. Piperacillin-tazobactam and carbapenems are active in vitro and would be appropriate initial therapy for serious *A. xylosoxidans* infections, whereas trimethoprim-sulfamethoxazole may be used for urinary tract and other infections not requiring parenteral therapy. Ceftazidime also has activity, although strains are generally resistant to other cephalosporins, narrow-spectrum penicillins, aztreonam, and aminoglycosides. Susceptibility to the fluoroquinolones is variable, and high rates of resistance to ciprofloxacin and aminoglycosides have been noted in strains isolated from cystic fibrosis patients. High concentrations of colistin inhibit most strains. Resistance mechanisms include a constitutive oxacillinase and acquired β-lactamases, as well as multidrug efflux pumps.[122] The presence of imipenemase (IMP)-, Verona integron–encoded (VIM)-, or Tripoli (TMB)-type metallo-β-lactamase genes carried on transferable class 1 integrons can produce carbapenem resistance and hold the potential for horizontal transfer.[123,124]

A. faecalis strains produce a distinctive odor resembling that of sweet apples and are usually susceptible to trimethoprim-sulfamethoxazole, ureidopenicillins, carbapenems, and (unlike *Achromobacter* species) most cephalosporins.[120] Results vary for aztreonam, fluoroquinolones, and aminoglycosides, with resistance to gentamicin being common.[120] Extended-spectrum β-lactamase production has also been described in *A. faecalis.*

Chryseobacterium and *Elizabethkingia* Species

Chryseobacterium species are inhabitants of soil and water and can be recovered from a variety of foods. They can be found in municipal water supplies despite adequate chlorination and have been recovered from the hospital environment, often in conjunction with clusters of clinical isolates. *Chryseobacterium* species are organisms of low virulence, and their presence in clinical specimens usually represents colonization and not infection. *C. indologenes* (formerly *Flavobacterium indologenes*) is the most frequently isolated species but is a rare cause of human disease. Most of the published cases have originated in Taiwan, with a few cases reported from Australia, Europe, India, and the United States. The majority of reported infections have been hospital acquired, and the vast majority of patients had undergone invasive procedures and had underlying conditions, such as neoplasms, diabetes mellitus, stem cell or solid-organ transplantation, or prolonged use of antibiotics. Reported infections include bacteremia, ventilator-associated pneumonia, cellulitis, peritonitis, indwelling device–associated infection, urinary tract infections, biliary tract infection, lumboperitoneal shunt infection, ocular infections, central nervous system infection, and surgical and burn wound infections. Infections have often been associated with a high mortality rate.[125]

Based on phylogenetic and phenotypic data, *C. meningosepticum* and *C. miricola* have been placed in the genus *Elizabethkingia* and are now known as *E. meningoseptica* and *E. miricola.*[126] In 2011, *E. anophelis* was described as a new species.[127] Cases of human infection due to *E. miricola* are rare. *E. miricola* has been isolated from respiratory and blood cultures of a stem cell transplant recipient with relapse of mantle cell lymphoma and from the urine of a pediatric patient with multiple comorbidities.[128,129]

E. meningoseptica has historically been the most frequently isolated species in the genus and is clinically significant in up to one-half of the adults and in about two-thirds of the neonates from whom it is recovered.[130] It is associated with both outbreaks and sporadic infections. In pediatric patients, neonatal meningitis is the most common presentation of *E. meningoseptica,* especially in premature infants during the first 2 weeks of life.[131] Clusters of neonatal meningitis have been linked to many sources, including contaminated saline solution for flushing eyes, respiratory equipment, and sink drains.[125,132] Neonatal meningitis is fatal in more than half the cases, and brain abscesses and other severe sequelae are common. Most *E. meningoseptica* infections in adults are hospital acquired and occur in immunocompromised hosts. The respiratory tract is the most common site of infection, and outbreaks have been linked to contaminated ventilator tubing and aerosols.[125] In outbreaks, respiratory tract colonization occurs more often than infection. Bacteremia is the second most common presentation of *E. meningoseptica* infection. In one cluster of bloodstream infections related to a contaminated anesthetic, the bacteremia was transient and systemic signs of infection resolved without specific antibiotic therapy, attesting to the low virulence of this organism in adults. *E. meningoseptica* has also caused endocarditis (including prosthetic valve endocarditis), cellulitis, wound infection, sepsis after extensive burns, abdominal abscess, dialysis-associated peritonitis, and endophthalmitis.[125,130] Other contaminated sources include contaminated syringes in ice chests, vials, sink drains, sink taps, tube feedings, flush solutions for arterial catheters, pressure transducers, and antiseptic solutions.[125,130,132] Infections including cellulitis, septic arthritis, community-acquired respiratory tract infection, keratitis, and bacteremia have been reported in the absence of underlying diseases.[125,130,133]

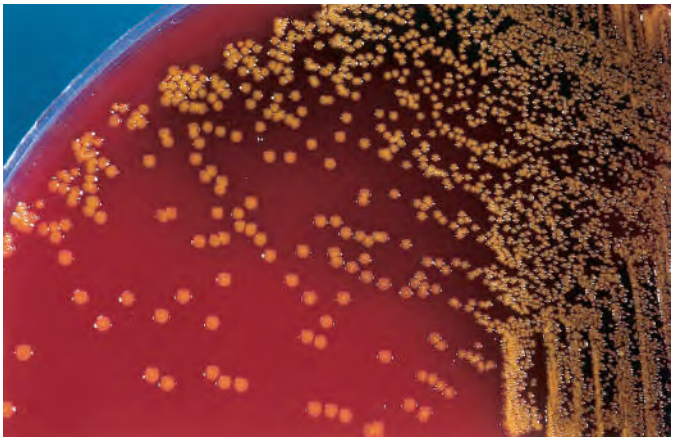

FIG. 236.2 **Pale yellow colonies of *Elizabethkingia meningosepticum* on blood agar plate.**

E. anophelis was first described in 2011 and reported to cause neonatal meningitis in 2013. Since then, several infections and outbreaks have been reported, including a 2015–2016 outbreak of 66 laboratory-confirmed infections in 63 patients in the United States, primarily in Wisconsin, and a separate report of 12 isolates from 11 patients in Illinois.[134] Most isolates were cultured from blood and caused disease in older patients with underlying comorbidities.[135]

Chryseobacterium and *Elizabethkingia* species may be long, thin, slightly curved, and occasionally filamentous on Gram stain. *C. indologenes* colonies usually form a dark-yellow to orange pigment in culture as a result of the production of the pigment flexirubin, whereas *E. meningoseptica* colonies are smooth, large, and pale yellow (Fig. 236.2). Both organisms grow well and form colonies within 24 hours on blood or chocolate agar and grow at a much slower rate, if at all, on MacConkey agar. They are not motile and produce positive catalase and oxidase reactions. *Chryseobacterium* can be distinguished from other nonfermenters by the ability to produce indole in tryptophan broth, but the reaction is often very weak. *Chryseobacterium* species produce proteases and gelatinase, which may contribute to virulence and are responsible for the greenish discoloration around the colonies on blood agar. *E. meningoseptica* has the ability to create biofilms, particularly in nutrient-rich conditions; isolates that produce higher quantities of biofilm have been associated with poor outcomes.[136] MALDI-TOF may be helpful in identification of *Elizabethkingia* isolates to the species level, but in one study species identification required amending the MALDI-TOF database.[137]

Chryseobacterium species and *E. meningoseptica* are resistant to most antibiotics, and the use of inactive drugs as empirical therapy may contribute to the poor outcome in many infections. Results of susceptibility testing vary when different methods are used; disk diffusion methods especially are unreliable, and broth microdilution should be employed, if possible.[138] Etest has also been suggested as a possible alternative for testing certain antibiotics.[139] *E. meningoseptica* and *Chryseobacterium* organisms produce β-lactamases and are naturally resistant to most β-lactam drugs, including carbapenems and aztreonam.[138,140] This resistance in *C. indologenes* has been shown to be due to chromosomally encoded class A extended-spectrum β-lactamase CIA, in addition to class B metallo-β-lactamase IND variants (IND-1 to IND-7 and IND-2a).[140,141] Three β-lactamase genes have been identified in *E. meningoseptica,* a class D serine-β-lactamase CME conferring resistance to cephalosporins and two unrelated wide-spectrum metallo-β-lactamases, BlaB (subclass B1) and GOB (subclass B3) with carbapenemase activity.[142] *E. meningoseptica* is unique in being the only reported microorganism with two intrinsic chromosomally encoded metallo-β-lactamases genes.[142] Cefepime has poor activity against *E. meningoseptica,* and only modest activity against *C. indolgenes.*[143] Tigecycline and piperacillin-tazobactam had similar activity against *E. meningoseptica,* with 88.5% of isolates being susceptible using US Food and Drug Administration breakpoints for Enterobacteriaceae.[144] *E. meningoseptica* is typically resistant to aminoglycosides, chloramphenicol, erythromycin, and colistin.[144] Fluoroquinolones are usually active in vitro, and sparfloxacin, cinafloxacin, and levofloxacin are somewhat more active than ciprofloxacin.[145] In two studies, minocycline was the only agent active against all *E. meningoseptica* strains.[130,138] Doxycycline and trimethoprim-sulfamethoxazole susceptibility was variable. Rifampin is active against most strains and has been used as part of combination therapy to clear persistent infection. Vancomycin, alone or in combination with other agents, including rifampin, has been successful in the treatment of meningitis in infants.[146] In some reported cases of meningitis treated successfully with vancomycin, the MICs of vancomycin were 8 to 12 μg/mL.[147] However, two groups reported that vancomycin was inactive in vitro (MICs of 16 to <64 μg/mL) and called into question the usefulness of vancomycin against *E. meningoseptica.*[130,138] Thus there is no optimal regimen for *E. meningoseptica* meningitis, and therapy should be based on properly performed susceptibility testing. Possible regimens include rifampin in combination with trimethoprim-sulfamethoxazole, a fluoroquinolone, or minocycline.

Comamonas and *Delftia* Species

Comamonas species are common environmental bacteria that occasionally cause human disease. Although these organisms are of low virulence and clinical significance is sometimes difficult to establish, some of their obscurity may be due to the inability of clinical laboratories to identify them; isolates may be reported as being nonfermentative gram-negative bacilli that could not be further identified.

Comamonas testosteroni, formerly *Pseudomonas testosteroni,* is the most common pathogen of the genus. In a review of 33 reported cases, the most common sites of infection were the bloodstream (13 cases), the peritoneal cavity (10 cases), and cerebrospinal fluid (3 cases).[148] Unusual sites of infection include urine, vitreous fluid, an infected animal bite wound, the embryonic cord of a stillborn infant of an intravenous drug–abusing mother, and pneumonia in a patient with immunodeficiency syndrome.[148] Many of these infections are polymicrobial.

Infections caused by *Delftia acidovorans* (formerly *Comamonas acidovorans* or *Pseudomonas acidovorans*) have been reported in immunocompetent and immunocompromised individuals as well as those with underlying disease.[149] These include keratitis and other ocular infections, bacteremia (including catheter-related bacteremia), endocarditis associated with intravenous drug use, otitis externa, peritonitis in a patient receiving peritoneal dialysis, hospital-acquired pneumonia, empyema, and urinary tract infection.[149] An outbreak of *D. acidovorans* bacteremia was linked to contaminated pressure-monitoring devices, but clinical and epidemiologic information was not provided.[148] Another species, *Delftia tsuruhatensis,* has also been reported as a cause of catheter-related infection.

Comamonas are strictly aerobic, motile, nonpigmented, oxidase-positive, gram-negative bacilli that grow well on routine bacteriologic media. Biochemical characteristics include accumulation of β-hydroxybutyrate, acetamide hydrolysis, and reduction of nitrate to nitrite. Most currently available identification systems will identify *Comamonas* to genus level, if at all. Species are distinguished by carbon compound use patterns. *Delftia* is phenotypically similar to *Comamonas.* Key differentiating characteristics include oxidation of fructose and mannitol and resistance to 10-μg colistin disks and 300-U polymyxin B disks.[150] There are no guidelines for antibiotic susceptibility testing for *Comamonas* or *Delftia* species. Published cases appear to indicate that *C. testosteroni* is more susceptible to common antibiotics than is *D. acidovorans.* Aminoglycosides, fluoroquinolones, carbapenems, piperacillin-tazobactam, and ceftazidime are potentially active. *D. acidovorans* is more resistant to aminoglycosides than *C. testosteroni* but is generally susceptible to broad-spectrum cephalosporins, piperacillin, aztreonam, carbapenems, quinolones, and trimethoprim-sulfamethoxazole.[150] Development of resistance to broad-spectrum penicillins and cephalosporins during antibiotic treatment has occurred.[150]

Eikenella Species

Eikenella corrodens is a fastidious facultative anaerobic gram-negative bacillus that is present as endogenous microbiota in the mouth and upper respiratory tract as well as on other mucosal surfaces. Although

it is recovered most often as a component of polymicrobial infection, commonly coexisting with streptococci, it has been recovered from sterile sites in pure culture.[151] Characteristic of *Eikenella* infection is an indolent course, generally taking more than 1 week from the time of injury to clinical manifestation of disease.[152] Many patients with *Eikenella* infection have underlying diseases, especially head and neck malignancies.[152] In case series and literature reviews, the head and neck were the most common sites of *Eikenella* infections in both adults and children.[151,152] Other common clinical manifestations include respiratory tract infections and human bite infections, infections among chronic finger or nail biters, and "clenched-fist injuries" following altercations. Because of the proximity of bone and joint spaces, these hand infections may lead to osteomyelitis and septic arthritis. The bacillus has been reported as a cause of ulceration after a human bite to the penis.[153] *Eikenella* has also caused infection in insulin-requiring diabetic patients and drug-abusing "skin poppers" who lick their needles,[154] and has caused necrotizing fasciitis after elective hernia repair.[155] Severe soft tissue infection, with or without underlying osteomyelitis, may be slow to resolve. Suppuration due to *Eikenella* infections is foul smelling, mimicking an anaerobic process. Pulmonary infections, including empyema, pneumonia, and septic emboli, in conjunction with internal jugular vein thrombosis (postanginal sepsis), can occur, typically in patients with underlying chronic illnesses or intrathoracic malignancies. Acute suppurative thyroiditis has occasionally been reported in adults and rarely in children. Gynecologic infections have been reported, including chorioamnionitis resulting in preterm labor and fetal demise and infection associated with intrauterine contraceptive devices.[156] *Eikenella* has also been recovered in pure culture from synovial fluid, bone, cerebrospinal fluid, brain, subdural and visceral abscesses, pleuropulmonary infection, and blood.[157,158] *E. corrodens* is another of the HACEK organisms, which have in common the need for incubation in an atmosphere enhanced with CO_2 for recovery in culture and a predilection for infecting the heart valves. Endocarditis caused by *E. corrodens* typically has an indolent course, but acute presentations are reported.[159] Endocarditis usually occurs after intravenous drug use or in patients with abnormal heart valves, including prosthetic valves, but infection of a structurally normal heart valve in a patient without predisposing risk factors has been reported.[12,160]

E. corrodens is a gram-negative, small straight rod that at times can appear pleomorphic or coccobacillary. It grows in either aerobic or anaerobic environments. It is nonmotile and non–spore forming and does not have a capsule. Cell surface components vary from strain to strain, and these differences may relate to virulence.[161] On blood or chocolate agar, even aided by the presence of 3% to 10% CO_2, the organism grows slowly, and it often requires 2 days or more to recognize the typical pinpoint colonies. Colonies are small and grayish (older colonies may become light yellow), produce a slight greenish discoloration on the blood agar, and elaborate an odor resembling that of bleach (hypochlorite). About half produce the pitting ("corroding") of the agar that is considered characteristic. The organism grows poorly on MacConkey agar. Strains do not form acid from carbohydrates; are oxidase positive, catalase negative (a few strains are weakly catalase positive), urease negative, and indole negative; and reduce nitrate to nitrite. Ampicillin, ureidopenicillins, second- and third-generation cephalosporins, and tetracyclines are active against *E. corrodens* in vitro and have been effective clinically.[156,162] The organism is susceptible to fluoroquinolones and azithromycin; however, it is uniformly resistant to clindamycin, erythromycin, and metronidazole and often resistant to aminoglycosides.[156,162] Because *Eikenella* infections are often polymicrobial, initial therapy with ampicillin-sulbactam or amoxicillin-clavulanate is appropriate in many cases, whereas ampicillin can be used for monomicrobial infections. Ceftriaxone is recommended for treatment of endocarditis caused by HACEK organisms because some of these gram-negative organisms produce β-lactamases. Although β-lactamase production in *Eikenella* is uncommon at present, these enzymes have been described.[163]

Flavobacterium and *Myroides* Species

The genus *Flavobacterium* consisted of a heterogeneous group of yellow-pigmented bacteria that did not prove to be closely related when subjected to genotypic analysis. Consequently, many *Flavobacterium* species, including the clinically important species, have been reclassified to other genera and are discussed elsewhere in this chapter. *Flavobacterium meningosepticum,* formerly the most important species, is now a member of the genus *Elizabethkingia,* whereas *Flavobacterium indologenes* is now in the genus *Chryseobacterium. Flavobacterium multivorum* and *Flavobacterium spiritivorum* now reside in the genus *Sphingobacterium. Flavobacterium odoratum,* an uncommon clinical isolate, has been placed in the genus *Myroides* and divided into two species, *M. odoratus* and *M. odoratimimus. Myroides* spp. are common in soil and water and are often not considered pathogenic. However, there are reports of clinical infections, including urinary tract infection, endocarditis, ventriculitis, cutaneous infections, pneumonia, bacteremia, septic shock, and soft tissue infections. These infections typically occur in severely immunocompromised patients, although rare severe infections have occurred in normal hosts.[164] Hospital-acquired infections are usually believed to originate from a hospital water source.[164] One outbreak of catheter-related bloodstream infections was traced to ampules of water contaminated with *M. odoratus* and *B. cepacia.*[165]

Myroides species are obligately aerobic and grow on most media, including MacConkey agar. Colonies are yellow and produce a fruity odor similar to that of *A. faecalis.* The organisms are nonmotile and are oxidase, catalase, urease, and gelatinase positive. They reduce nitrite and do not produce indole. Isolates are successfully identified to the genus level using VITEK 2 and MALDI-TOF, which is able to distinguish *M. odoratus* and *M. odoratimimus.*[164,166] *Myroides* are broadly resistant to β-lactams, including carbapenems, with variable susceptibility to aminoglycosides, quinolones, and sulfamethoxazole.[164,166] Cutaneous as well as systemic infections have been successfully treated with a quinolone, carbapenem, or trimethoprim-sulfamethoxazole based on the results of in vitro susceptibility testing.[164] Analysis of the genome of an *M. odoratimimus* strain isolated from a patient with urinary tract infection revealed several resistance genes.[167]

Additional *Myroides* species isolated from clinical cultures but of unclear significance include *Myroides phaeus,* isolated from the saliva of a student in China,[168] and a newly described species, *Myroides injenensis,* isolated from urine.[169]

Ochrobactrum Species

Organisms formerly called CDC group Vd and *Achromobacter* groups A, C, and D were renamed *Ochrobactrum anthropi* (Gr. *ochros,* "pale yellow").[170] Studies suggest that *Achromobacter* group C and some group A strains belong to a distinct species now designated as *O. intermedium.*[170] *O. anthropi* has been recovered from the environment and clinical sources. Published reports suggest that this organism is an emerging pathogen in immunocompromised patients and that infections caused by this organism may be increasing in frequency.

Intravascular catheter–related bacteremia is the most common infection associated with *O. anthropi.*[171,172] This organism has contaminated biologic products, which have been the source of small outbreaks. Five bloodstream infections occurred in organ transplant recipients who received contaminated rabbit antithymocyte globulin.[173] Consistent with the low virulence of this organism, bacteremia resolved in four of five immunosuppressed patients in this series without antibiotic administration. Three patients developed *O. anthropi* urinary tract infections following transrectal ultrasound–guided prostate biopsies.[174] Three cases of postoperative meningitis in neurosurgical patients were traced to cadaveric pericardial patches possibly contaminated during processing.[175] *O. anthropi* has been cultured from tap water at a hematology unit in association with a small outbreak.[176] It has been reported to cause bacteremia in patients on hemodialysis, in patients with AIDS, and in liver transplant recipients and peritonitis in patients undergoing continuous ambulatory peritoneal dialysis.[177–180] *Ochrobactrum* endophthalmitis has occurred after hematogenous spread and postoperatively, including a cluster of nine cases after cataract extraction with lens implantation.[181] Other reported infections include infection of pacemaker leads, prosthetic valve endocarditis, pancreatic abscess, pelvic abscess complicating appendicitis, necrotizing fasciitis, septic arthritis, and osteochondritis after a puncture wound.[182] It has also been recovered from bile, urine, wounds, stool, throat, and vagina.[183] There is a single case report of *Ochrobactrum tritici* causing

bacteremia and cholecystitis. This isolate was misidentified by both MALDI-TOF and biochemical tests as *O. anthropi,* with the species identification made by 16S rRNA sequencing.[184]

O. anthropi is an oxidase-positive, non–lactose-fermenting gram-negative bacillus that grows readily on MacConkey agar. The organism oxidizes glucose and xylose, but 72 hours or more of incubation may be required before this is apparent. *O. anthropi* is motile by means of peritrichous flagella, which helps to differentiate it from pseudomonads and *Chryseobacterium.* The organism is similar to *A. xylosoxidans* subsp. *xylosoxidans* in biochemical characteristics, but it can hydrolyze urea and grows poorly on cetrimide agar.[107] *O. anthropi* and *O. intermedium* are closely related to *Brucella* species. Routine biochemical tests and automated identification systems are not reliable and are prone to misidentification; at best, these systems provide identification to the genus level.[185] *O. anthropi* is usually susceptible to trimethoprim-sulfamethoxazole and fluoroquinolones, both of which should be considered appropriate initial therapy. Isolates are variably susceptible to gentamicin, amikacin, netilmicin, imipenem, and tetracycline and generally resistant to β-lactams, including most cephalosporins and penicillins, at least in part as a result of the presence of an AmpC β-lactamase.[185] Failures with imipenem therapy have been reported.

Oligella Species

The genus *Oligella* was named for the small size of the bacilli on Gram stain and contains two species, *Oligella urethralis* (formerly *Moraxella urethralis* and CDC group M4) and *Oligella ureolytica* (formerly known as CDC group IVe). *O. urethralis* is a commensal of the genitourinary tract, and most clinical isolates are from the urine, predominantly from men. Although symptomatic infections are rare, bacteremia, septic arthritis mimicking gonococcal arthritis, and peritonitis in two patients receiving chronic ambulatory peritoneal dialysis[186] have been described. *O. ureolytica* is also primarily found in the urine, usually from patients with long-term indwelling urinary catheters or other urinary drainage systems. These patients have a propensity to develop urinary stones that may be related to the ability of the organism to hydrolyze urea and alkalinize the urine, leading to precipitation of phosphates. Bacteremia has been reported in patients with obstructive uropathy.[187] *O. ureolytica* bacteremia has been reported in a patient with AIDS and infected decubitus ulcers.

Oligella species, especially *O. urethralis,* resemble *Moraxella* and appear coccobacillary on Gram stain. Most strains will grow on blood or MacConkey agar but require extended incubation (2–4 days) before growth can be detected. *O. urethralis* is nonmotile, whereas most strains of *O. ureolytica* are motile by peritrichous flagella. The rapidity of the urease reaction (within 5 minutes on a Christensen urea agar slant) is a distinctive feature of *O. ureolytica.* These organisms are oxidase positive and catalase positive and reduce nitrate to nitrite. Contemporary data on antimicrobial susceptibilities are sparse. Strains of *O. urethralis* are usually susceptible to β-lactam antibiotics, but β-lactamase–producing strains, as well as strains resistant to ciprofloxacin, have been reported.[186] Resistance to β-lactam antibiotics is due to acquisition of chromosomally encoded AmpC β-lactamases, either ADC-7 or ABA-1, derived from *Acinetobacter baumannii.*[188,189]

Pseudomonas Species

The genus *Pseudomonas* has been modified considerably and now contains the organisms previously known as *Flavimonas oryzihabitans* and *Chryseomonas luteola.*[190] These organisms are included in the nonfluorescent group of pseudomonads that includes *P. stutzeri* and other rarely encountered species. The fluorescent group contains *P. fluorescens, P. putida,* and *P. aeruginosa. P. aeruginosa* is the only member of the genus that possesses significant virulence factors and is an important human pathogen; it is discussed in Chapter 219. Members of the fluorescent group produce pyoverdin, a yellow-green pigment that fluoresces under ultraviolet light. Pseudomonads are environmental organisms and have a predilection for moist environments. They can contaminate solutions such as distilled water, disinfectants, and intravenous solutions. Not surprisingly, many of the infections caused by these organisms are health care–associated. *P. fluorescens* species complex contains ~20% of the *Pseudomonas* species.[191] *P. fluorescens* is considered to be of low virulence and an uncommon cause of human infection. Most infections have been hospital acquired and have involved immunocompromised patients. Reported outbreaks include catheter-associated bacteremia, pseudobacteremia due to contaminated blood collection tubes, peritonitis in peritoneal dialysis transplant patients, and febrile neutropenia associated with a contaminated drinking water dispenser in a bone marrow transplantation unit.[192] Contaminated heparin flush solution caused a large multistate outbreak of *P. fluorescens* catheter-related bacteremia; in some exposed patients with implanted ports, diagnosis was delayed for many months after exposure to the solution.[193] This organism can grow at 4°C, allowing it to proliferate in contaminated blood products and occasionally cause transfusion-related sepsis.[194] *P. fluorescens* can be misidentified by commercial laboratory systems. Because isolation of this organism can reflect pseudobacteremia, proper identification is important to avoid unnecessary antimicrobial therapy.

P. putida is also an occasional cause of health care–associated bacteremia in patients with cancer, pneumonia, peritonitis, urinary tract infections, and neonatal sepsis.[195,196] In an outbreak of *P. putida* catheter-related bacteremia caused by a contaminated flush solution, infection was cured without catheter removal in most patients.[197] Isolation of this organism from clinical specimens can reflect contamination; it has also been associated with pseudo-outbreaks. *P. stutzeri* is another uncommon clinical isolate that has been reported to cause bacteremia, nosocomial brain abscess, and meningitis in immunocompromised hosts.[198] Rare cases of community-acquired osteomyelitis, septic arthritis, conjunctivitis, pneumonia, and peritoneal dialysis–related peritonitis have also been reported.[199] *P. stutzeri* has also been implicated as a cause of pseudobacteremia and of delayed-onset endophthalmitis after cataract surgery as well as an unusual case of relapse of endocarditis 4 years after the initial episode.[199,200] *Pseudomonas mendocina* has occasionally caused bacteremia and endocarditis.[201]

Pseudomonas oryzihabitans (L. *oryza* + *habitans,* "inhabiting rice") is the current name for the organism that at various times has been called *Chromobacterium typhiflavum, Flavimonas oryzihabitans,* and CDC group Ve-2.[202] It is an infrequent cause of infection with characteristics similar to those of *P. luteola. P. oryzihabitans* is normally found in soil, water, and damp environments such as rice paddies. In the hospital setting, it has been recovered from sink drains and respiratory therapy equipment.[202] Central venous catheter–associated bloodstream infection is the most commonly reported infection. In an 8-year study from a major cancer center, 21 of 22 episodes of *P. oryzihabitans* bacteremia were catheter related.[203] In this series, most infections were non–hospital acquired, polymicrobial infections were common, and most bacteremias could be treated without catheter removal. In contrast, in another series, all *P. oryzihabitans* bacteremias were hospital acquired and the implicated intravascular devices were removed in most cases.[204] The organism has also been associated with other foreign bodies, such as peritoneal dialysis catheters, ventriculostomy tubes, vascular grafts, prosthetic joints, and intraocular lenses.[205,206] Soft tissue infections, postoperative wound infections, splenic abscesses, and meningitis have been reported.[207,208] Although most patients with *P. oryzihabitans* infection are immunocompromised, the infections are indolent and recovery is the rule. *Pseudomonas luteola* is another uncommon opportunistic pathogen. It was previously known as CDC group Ve-1 and *Chryseomonas luteola. P. luteola* infections are often associated with foreign bodies such as central venous and peritoneal dialysis catheters. Reported infections include bacteremia, peritonitis (associated with appendicitis and colon cancer as well as catheters), osteomyelitis, endocarditis, leg ulcers, cellulitis, postoperative endophthalmitis, and meningitis and brain abscesses.[205,207,209,210]

Pseudomonas species are aerobic, non–spore-forming, gram-negative rods. They are motile owing to the presence of one or more polar flagella. They are lactose nonfermenters and grow well on MacConkey agar. Most clinical isolates (except *P. luteola* and *P. oryzihabitans*) are oxidase positive. In addition to the negative oxidase reaction, these two species produce yellow-pigmented colonies on MacConkey agar that help distinguish them from other pseudomonads. Unlike other fluorescent pseudomonads, including *P. aeruginosa, P. fluorescens* and *P. putida* do not reduce nitrate and oxidize xylose. *P. stutzeri* colonies are brown, dry, and wrinkled on primary isolation media.

There are limited antimicrobial susceptibility data for these pseudomonads. *P. putida* can show broad resistance to β-lactam antibiotics, and some isolates of this organism produce a metallo-β-lactamase that can readily hydrolyze carbapenems.[211] *P. oryzihabitans* is usually susceptible in vitro to ureidopenicillins, third-generation cephalosporins, aztreonam, imipenem, aminoglycosides, fluoroquinolones, and trimethoprim-sulfamethoxazole but shows resistance to earlier-generation cephalosporins.[203,212] Clinical isolates of *P. luteola* are often resistant to first- and second-generation cephalosporins, tetracyclines, ampicillin, and trimethoprim-sulfamethoxazole but are susceptible to third-generation cephalosporins, imipenem, aminoglycosides, and quinolones.[205] A high proportion of clinical *P. putida* strains harbor metallo-β-lactamases on transposable elements that can potentially disseminate and contribute to multidrug resistance in other organisms.[211]

Ralstonia and *Cupriavidus* Species

The genus *Ralstonia* was established in 1995 and initially contained one recognized pathogen, *Ralstonia pickettii* (formerly *Pseudomonas,* then *Burkholderia, pickettii*). Subsequently, several other clinically relevant species were added to the genus, including *Ralstonia paucula* (formerly designated as CDC group IVc-2), *Ralstonia gilardii,* and, most recently, *Ralstonia mannitolilytica* (formerly *Pseudomonas thomasii,* then *R. pickettii* biovar 3/*"thomasii"*). There was extensive taxonomic revision of the genus in 2004, with *R. pickettii* and similar organisms remaining in the genus *Ralstonia,* but species in the *R. eutropha* lineage, including *R. paucula* and *R. gilardii,* were transferred to the new genus *Wautersia.* 16S rRNA profiles quickly revealed that the newly named *Wautersia* organisms were synonymous with the existing genus *Cupriavidus,* which, according to nomenclature rules, has priority over the genus name *Wautersia,* and all species that had been placed in the genus *Wautersia* were transferred to the genus *Cupriavidus. Ralstonia* and *Cupriavidus*[213,214] species are environmental gram-negative, nonfermentative bacilli of low virulence. *Cupriavidus* have also been found as abnormal microbiota in the respiratory tract of patients with pulmonary tuberculosis and on the skin of patients with psoriasis.[213,214] Reported infections caused by *Ralstonia* and *Cupriavidus* are related to contaminated infusates or occur in immunocompromised hosts, including transplant recipients and patients with HIV infection or leukemia.[215]

R. pickettii can grow in saline and other fluids and has been the cause of many outbreaks related to contaminated infusates and pseudo-outbreaks related to contaminated solutions used in laboratory diagnosis.[216,217] The contamination of solutions has occurred during the manufacturing process and by extrinsic manipulation. In addition to bacteremia from contaminated intravenous products, airway colonization has been caused by contaminated respiratory therapy solutions.[217] In one outbreak due to a contaminated saline solution, only 1 of 19 patients with *R. pickettii* airway colonization received antimicrobial therapy, consistent with the low virulence of the organism.[217] Several hospital-associated outbreaks attributed to *R. mannitolilytica* have also been described.[218,219] Clinical isolates of other *Ralstonia* and *Cupriavidus* species are less common. A number of *Ralstonia* and *Cupriavidus* species have been isolated from sputum cultures of cystic fibrosis patients.[220,221] Most of the reported human infections of *C. pauculus* and *C. gilardii* are intravascular catheter–related bloodstream infections.[222] *C. pauculus* has been recovered in cases of peritoneal dialysis–associated peritonitis, tenosynovitis after a cat bite,[223] pneumonia in immunocompetent patients, a pseudo-outbreak from contaminated culture swabs, and two reports of bacteremia in patients on extracorporeal membrane oxygenation with a contaminated thermoregulatory reservoir as the source.[224] Reports of infection caused by *C. metallidurans* include septicemia in a patient with multiple comorbidities and catheter-related bacteremia.[225,226] Most patients have responded well to antibiotic therapy.

Ralstonia and *Cupriavidus* species grow on routine media, although growth may be slow and require more than 72 hours of incubation to visualize colonies. *Ralstonia* species have one or more polar flagella in motile species, produce acid from glucose and several other carbohydrates, and are resistant to colistin, whereas *Cupriavidus* species have peritrichous flagella, do not produce acid from glucose, and are susceptible to colistin. Extensive biochemical testing is required for identification, and misidentification of these organisms by commercially available systems is common.[219] Identification may also be confused because *R. pickettii, R. mannitolilytica,* and *R. insidiosa* are able to grow on selective media intended for isolation of *B. cepacia.* 16S rRNA PCR and MALDI-TOF mass spectrometry have been useful means of identification.[220,221]

There are no validated in vitro susceptibility testing methods for *Ralstonia* species or *Cupriavidus* species. *R. pickettii,* but not other *Ralstonia* or *Cupriavidus* species, produces a chromosomally encoded class D oxacillinase β-lactamase, OXA-22, that confers resistance or reduced susceptibility to aminopenicillins, narrow-spectrum cephalosporins, and aztreonam.[227] An inducible chromosomal oxacillinase β-lactamase, OXA-60, that hydrolyzes imipenem is also widespread.[227] Isolates of *R. pickettii* have been reported to be generally susceptible to the ureidopenicillins, ciprofloxacin, and trimethoprim-sulfamethoxazole, with varied susceptibility to aminoglycosides.[228] *R. mannitolilytica* is often resistant to ampicillin, aminoglycosides, and aztreonam. *C. pauculus* is reportedly susceptible to many β-lactams, along with quinolones and tetracycline, but is often resistant to aminoglycosides.[215,222]

Rhizobium (Formerly *Agrobacterium*) Species

Based on 16S ribosomal DNA analysis, organisms previously known as *Agrobacterium, Allorhizobium,* and *Rhizobium* are now unified into a single genus, *Rhizobium.* These organisms are well-known plant pathogens; most contain a large tumor-inducing plasmid, and infection produces neoplastic growth in many plant species. They are present in soil and plants and have a worldwide distribution. Although most clinical isolates appear nonpathogenic, there have been more than 50 reported cases of human disease caused by *Rhizobium* species, primarily *R. radiobacter* and, more rarely, *Agrobacterium tumefaciens.* However, *A. tumefaciens* and *R. radiobacter* differ only by the presence or absence of the tumor-inducing plasmid, and they are now combined into a single species, *Rhizobium radiobacter.* Recent reports suggest that the newly named species, *Rhizobium pusense,* distinguishable from *R. radiobacter* only by 16S rRNA sequencing, is the main human pathogen of this genus.[229,230]

More than half of the reported cases of *R. radiobacter* infection are intravascular catheter–related bloodstream infections in compromised hosts, primarily patients with malignancies.[231] Most of these infections were not hospital acquired. However, there is a report of three cases of *R. radiobacter* (reported as *Agrobacterium* spp.) bacteremias occurring at a single institution in patients with tunneled intravenous catheters.[232] Two of these cases were epidemiologically linked, and the isolates had common pulsed-field gel electrophoresis patterns suggesting nosocomial transmission.[232] Other opportunistic infections associated with *R. radiobacter* include pneumonia, urinary tract infections, peritonitis, cellulitis, wound infections, cerebral abscess, and endocarditis.[233] Most of these infections occurred in hospital settings or in immunosuppressed patients or involved a device, the removal of which has been necessary in some cases to effect a cure. *R. radiobacter* has also caused pseudobacteremia resulting from contaminated citrated tubes used for clotting factor studies.[234] Several cases of postoperative endophthalmitis occurred in patients, some of whom reported outdoor activities such as gardening or golfing that may have exposed them to soil bacteria.[235] In most cases, the source of the infecting organisms is unknown. Consistent with this organism being an opportunistic pathogen of low virulence, all patients have survived.

The organism readily grows on blood agar and MacConkey agar when incubated aerobically. Colony appearance varies for the different species. Flagellar stains show peritrichous distribution. Organisms are oxidase positive and catalase positive, and they produce gas from a variety of carbohydrates, including lactose. Rapid hydrolysis of urea and slower hydrolysis of esculin are key features that help to distinguish this organism from *Alcaligenes* species and *Pseudomonas* species, which it otherwise closely resembles. Ambiguous or erroneous identifications occur with standard identification systems, and identification often requires 16S rRNA sequencing. Clinical as well as environmental isolates have been reliably identified using MALDI-TOF mass spectrometry. Clinical isolates have been variably susceptible to antibiotics and display variations in susceptibility patterns within classes of antibiotics. Reported *R. radiobacter*

strains have universally been susceptible to fluoroquinolones, cefepime, and carbapenems, and these agents should be considered for initial therapy. Acquired resistances are common for other β-lactam antibiotics and aminoglycosides, with gentamicin being more active than tobramycin. Monobactams are produced by some soil strains; not surprisingly, clinical isolates are often resistant to aztreonam.

Roseomonas Species and Other "Pink-Pigmented" Gram-Negative Bacilli

The group of organisms previously known as CDC "pink coccoid" groups I through IV have been placed in the genus *Roseomonas* (L. *roseus* + *monas,* "a rose-colored or pink bacterium"). Although *Roseomonas* species can be recovered from the environment, most named *Roseomonas* species, including *R. gilardii* subsp. *gilardii, R. gilardii* subsp. *rosea, R. cervicalis,* and *R. mucosa,* have been isolated from clinical specimens.[236] *Roseomonas* appears to cause more clinical disease than the related pink-pigmented bacterium *Methylobacterium.*[237] *Methylobacterium* species, which are so named because of their ability to facultatively use methane, were previously classified under such names as *Pseudomonas mesophilica, Protomonas extorquens, Protaminobacter rubra,* "the pink phantom," and *Vibrio extorquens.*[238] The two most clinically relevant species, *M. mesophilicum* and *M. zatmanii,* are very similar phenotypically, and some reference laboratories limit identification to the genus level only.[238]

R. gilardii is usually recovered in pure culture and, in one retrospective series, appeared to cause clinical illness more often than not.[237] Infections are often community acquired. Bloodstream infection is the most common presentation and may be related to the presence of intravascular catheters[239] or may be secondary to processes at other sites, including intraabdominal abscesses, and respiratory tract or urinary tract infections. These infections usually, but not invariably, occur in patients with underlying medical illnesses such as malignancies, AIDS, chronic renal disease, or diabetes. Device removal may be necessary to clear intravascular catheter–related bacteremia. Peritoneal dialysis–associated peritonitis, vertebral osteomyelitis, ventriculitis, septic bursitis, soft tissue infections, epiglottitis, postoperative endophthalmitis, and postoperative septic arthritis have also been reported.[237,240–244] Thirty-six episodes of *Roseomonas* bacteremia occurred in one referral cancer center over a 12-year period, with *R. mucosa* causing 61% of these infections.[245] Most patients had central venous catheters; line removal was necessary in six patients to clear the bloodstream infection. Most of the isolates were initially misidentified or unidentifiable; *Roseomonas* infection was confirmed by supplemental testing, including 16S rRNA genotypic studies. *R. fauriae* is rarely isolated from clinical specimens but has been reported to cause peritonitis in a patient undergoing continuous ambulatory peritoneal dialysis.[246] *R. mucosa* septic arthritis has been reported in a patient with rheumatoid arthritis undergoing treatment with infliximab.

Methylobacterium has also caused intravascular catheter–related bacteremia, peritonitis in patients receiving continuous ambulatory peritoneal dialysis, and soft tissue infections.[247] A pseudo-outbreak of *Methylobacterium* respiratory tract infections was traced to contaminated tap water in the bronchoscopy suite.[248]

Roseomonas species are plump gram-negative rods or coccobacilli. In contrast, *Methylobacterium* species do not stain well and can appear gram variable, and also have intracellular vacuoles. Colonies are pink pigmented and are sometimes mucoid. Both these organisms can appear weakly oxidase positive and are catalase positive and urease positive. *Roseomonas* can be distinguished from *Methylobacterium* by the inability to oxidize methanol, the inability to assimilate acetamide, and the absence of long-wave ultraviolet light absorption. *Methylobacterium* has been isolated after 1 week of incubation on medium ordinarily used for the isolation of mycobacteria.[241]

Carbapenems, aminoglycosides, and tetracyclines are the most active antibiotics against *Roseomonas* species.[242,245,249,250] These organisms generally have high MICs to penicillins and cephalosporins, with the exception of β-lactamase inhibitor combinations, which are frequently but not invariably active. *Roseomonas* species usually have low MICs to fluoroquinolones but high MICs to trimethoprim-sulfamethoxazole.[250]

Methylobacterium grows slowly, and susceptibility testing is not always possible.[238] Many *Methylobacterium* isolates produce a β-lactamase, and the organisms have high MICs to penicillins and many cephalosporins. Aminoglycosides, ciprofloxacin, and trimethoprim-sulfamethoxazole are active.

Shewanella Species

Shewanella putrefaciens (formerly *Pseudomonas putrefaciens, Alteromonas putrefaciens,* or CDC group Ib) is widely distributed in the environment and has infrequently been implicated as a cause of human disease. *Shewanella* can be recovered from a variety of water sources, natural gas and petroleum reserves, dairy products, meat, and fish. Most reported human *Shewanella* infections have been attributed to *S. putrefaciens.* However, the automated and semiautomated identification systems used have not been able to differentiate between *S. putrefaciens* and *S. algae* because *S. algae* is not included in the databases.[251] When additional phenotypic or genotypic characteristics are considered, most human infections are realized to be caused by *S. algae.*[251] Cases of human infection attributed to *S. haliotis* and *S. xiamenensis* have also been reported.[252] *Shewanella* is frequently isolated as part of a polymicrobial infection, most often with enteric organisms, and its pathogenic role is often unclear. *Shewanella* is most commonly isolated from intraabdominal specimens, skin and soft tissue specimens, blood, and sputum.[253–255] Malignancy, hepatobiliary disease, diabetes mellitus, and colonization of the biliary tract are common underlying conditions. Cellulitis of the lower extremity in association with chronic ulcers or after burns is one of the more commonly described presentations.[253] Exposure to seawater is also a commonly reported risk factor.[256,257] An unusual case of *Shewanella* wound infection occurred following a cobra snakebite and required amputation of the infected finger.[258] *Shewanella* bacteremia, which also is frequently polymicrobial, can accompany soft tissue infection or biliary tract disease or occur in compromised hosts.[254] Compromised hosts are more likely to have accompanying signs of sepsis and have a poor outcome. A common source outbreak that led to 31 patients infected or colonized by *Shewanella* on a surgical ward was traced to a contaminated shared measuring cup.[259] In this outbreak, blood, bile, and ascitic fluid were the most common culture isolation sources. Bacteremia and respiratory distress have been described in neonates and premature infants.[254] Bacteremia following consumption of raw fish in a patient with end-stage renal disease has been reported.[260] Less commonly reported infections include peritonitis, pneumonia, empyema, purulent pericarditis, meningitis, brain abscess, osteomyelitis, otitis, urinary tract infection, endophthalmitis, keratitis, infected aortic aneurysm, and flexor tenosynovitis.[251,253–255,261]

On Gram stain, *Shewanella* is a short to long gram-negative rod and can be filamentous. It grows readily and produces small to medium-sized colonies that have a yellow-orange or brown-to-tan soluble pigment that causes greenish discoloration of the medium. Colonies may be mucoid and have a fishlike smell. *Shewanella* is oxidase positive and is the only nonfermenter that produces hydrogen sulfide on triple sugar iron agar, a key feature that allows easy identification in the laboratory. *S. algae* can be distinguished from *S. putrefaciens* by growth at 42°C, growth in 6.5% NaCl, mucoid colonies, weak β-hemolysis on sheep blood agar, reduction of nitrite, and the inability to produce acid from sucrose, maltose, and L-arabinose.[251] With current databases, MALDI-TOF mass spectrometry accurately identifies isolates to the genus level, but species identification is currently problematic.[262]

Putative virulence factors in *S. algae* that enable severe infection include production of a hemolysin and exotoxin, ability to adhere to epithelial cells, and biofilm formation.[256] *Shewanella* is also resistant to many heavy metals and antiseptic agents, which allows survival in harsh environments.[256]

β-Lactamases and multidrug efflux pumps have been detected that contribute to high MIC values for some antibiotics.[256] *Shewanella* is reported as resistant to penicillin and cefazolin but susceptible to most third- and fourth-generation cephalosporins and piperacillin.[255] The organisms are also usually susceptible to aminoglycosides, chloramphenicol, erythromycin, and quinolones but less predictably susceptible to tetracycline and trimethoprim-sulfamethoxazole.[251,253,254,263,264] Carbapenem-resistant strains have been reported.[264] *Shewanella* may

also contain a chromosomally encoded gene, *qnr3,* that confers resistance to quinolones by protecting DNA gyrase and probably also topoisomerase IV.[264] Because *Shewanella* is often recovered as part of a polymicrobial intraabdominal infection, piperacillin-tazobactam is reasonable initial therapy. However, development of resistance while on treatment has been reported with piperacillin-tazobactam and imipenem.[263]

Sphingobacterium Species

The genus *Sphingobacterium* includes organisms previously classified as *Flavobacterium* species. The organisms that were transferred to this genus contain large amounts of sphingophospholipid compounds in their cell membranes and have other taxonomic features that distinguish them from flavobacteria. Most isolates from humans are *S. multivorum* or *S. spiritivorum*. Most cases of *S. multivorum* infection are hospital acquired, but the natural habitat of the organism is not well defined. The reported cases of *S. multivorum* have been associated with peritonitis, septicemia, bacteremia, chronic respiratory infection in patients with underlying conditions, and colonization of the airway in patients with cystic fibrosis. It has also been recovered from contact lens storage cases from patients with corneal infiltrative events.[265] Also reported is an unusual case of necrotizing fasciitis and septic shock in an immunocompromised patient following a scratch to the leg by the patient's dog.[266] *S. spiritivorum* has been rarely recovered from clinical specimens, primarily urine and blood.[267] Cellulitis presumably from soil contact with secondary bacteremia and dialysis catheter–related bacteremia have been reported, as has hypersensitivity pneumonitis related to a water source harboring *S. spiritivorum*.[268–270]

S. multivorum and *S. spiritivorum* are straight gram-negative rods that are strictly aerobic; grow on blood agar but are limited or absent on MacConkey agar; are DNAase, oxidase, catalase, and urease positive and indole negative; and produce light-yellow colonies. Automated systems and the API 20 NE system (bioMérieux, Durham, NC) produce reliable identifications. *Sphingobacterium* species are intrinsically resistant to many commonly employed antibiotics and can grow in some antiseptics and disinfectants.[271] *S. multivorum* can produce an extended-spectrum β-lactamase and a metallo-β-lactamase conferring resistance to third-generation cephalosporins and carbapenems, respectively.[272] Trimethoprim-sulfamethoxazole and quinolones appear to be active. The combination of trimethoprim-sulfamethoxazole and perfloxacin produced cure in a bacteremic patient.[271] A bacteremic patient receiving hemodialysis improved clinically after receiving ampicillin and one dose of tobramycin, despite in vitro testing showing ampicillin resistance. The combination of surgical débridement and amoxicillin-clavulanate was effective in the reported necrotizing fasciitis case.[266] *S. spiritivorum* tends to be more susceptible, with ceftazidime, carbapenems, trimethoprim-sulfamethoxazole, and quinolones appearing active in vitro.

Sphingomonas Species

The genus *Sphingomonas* contains at least 95 species, of which only one, *Sphingomonas paucimobilis,* is an occasional human pathogen.[273] This organism, formerly known as *Pseudomonas paucimobilis* and CDC group IIk-1, is widely distributed in soil and water, including water sources in the hospital environment. Most *Sphingomonas* infections are hospital acquired and typically occur in immunocompromised individuals. Central catheter–related bacteremia, bacteremia due to a contaminated intravenous medication, peritoneal catheter–associated peritonitis, meningitis, ventriculoperitoneal shunt infection, brain abscess, soft tissue infection, wound infection, postoperative endophthalmitis, adenitis, urinary tract infection, and a variety of visceral abscesses have been reported.[274–279] Although ventilator-associated pneumonia has been described,[280] airway colonization was much more common than infection in intensive care unit outbreaks.[280,281] *S. paucimobilis* is considered to be an organism of low virulence, likely owing to the absence of endotoxins, but infection can lead to septic shock. Sporadic reports of unusual invasive and severe infections include septic arthritis and osteomyelitis, respiratory tract infections in cystic fibrosis patients, and necrotizing soft tissue infections.[277,282] Diabetes mellitus and alcoholism appear to be risk factors for community-acquired *S. paucimobilis* infections, including bacteremia.[278]

S. paucimobilis is a polymorphic gram-negative rod and is strictly aerobic, weakly oxidase positive, and catalase positive. Colonies grow on blood agar but not MacConkey agar and produce a yellow pigment. Despite the presence of a single polar flagellum, a low percentage of cells are actively motile, and motility can be difficult to demonstrate in the laboratory (thus the name *paucimobilis*).[283] *Sphingomonas* may be misidentified by conventional identification systems but is correctly identified by MALDI-TOF mass spectrometry.

The most effective antibiotics appear to be broad-spectrum β-lactam antibiotics, β-lactam–β-lactamase inhibitor combinations, cephalosporins, fluoroquinolones, and carbapenems.[282] Patients have been noted to respond well, even debilitated hosts and in cases when empirical treatment did not correlate with subsequent susceptibility tests.[276] The importance of removing the catheter to ensure complete eradication of the organism and to prevent recurrence of intravascular catheter–associated bloodstream infections is stressed in several reports.[276]

Weeksella and *Bergeyella* Species

The genus *Weeksella,* when proposed in 1986, contained two species, *W. zoohelcum* (CDC group IIj) and *W. virosa* (CDC group IIf), that differed from most nonfermentative gram-negative bacilli in being susceptible to penicillin. *W. zoohelcum* has been moved to the new genus *Bergeyella. Bergeyella zoohelcum* (Gr. "animal" + "wound") is part of the normal oral microbiota of dogs and other animals, and most clinical isolates come from bite wounds.[284–286] The organism was also isolated from a soft tissue infection in an injured tsunami survivor.[287] There are a few case reports of invasive *B. zoohelcum* infections, including meningitis, infective endocarditis, and bacteremia; some have occurred after dog bites or lengthy exposure to pets.[285,288] A 44-year-old woman developed *B. zoohelcum* bacteremia 1 day after eating a meal prepared with goat blood.[289] A proposed new species, *B. cardium,* was isolated from patients with infective endocarditis in Korea.[290] *W. virosa* has been isolated predominantly from the genital tract and urine of women and is usually not a pathogen. There are case reports of dialysis-associated peritonitis, spontaneous bacterial peritonitis, presumed dialysis catheter–related bacteremia and sepsis, overwhelming sepsis and pneumonia, and intracranial infection.[291] All infected patients had significant comorbidities.

Both *Bergeyella* and *Weeksella* generally grow well on blood agar, but some strains of *Bergeyella* grow better on chocolate agar. Both organisms do not grow on MacConkey agar. They are oxidase positive, catalase positive, indole positive, and nonpigmented. In contrast to *W. virosa, B. zoohelcum* produces urease and is resistant to polymyxin. *W. virosa* (L., "slimy") forms mucoid colonies that stick tenaciously to agar surfaces. Both species have low MICs to β-lactam antibiotics, including penicillin, chloramphenicol, and fluoroquinolones, and have variable MICs to tetracycline and trimethoprim-sulfamethoxazole; many of these agents have been used successfully in case reports. *W. virosa* is usually resistant to one or more aminoglycosides. The combination of penicillin susceptibility and aminoglycoside resistance is a clue to the identification of this organism. *Bergeyella* has been misidentified by automated commercial systems, but MALDI-TOF mass spectrometry has been successfully used to identify these organisms.[285]

Centers for Disease Control and Prevention Groups

The CDC Special Bacteriology Reference Laboratory receives unusual isolates from state laboratories and other reference laboratories. Some of these isolates are unnamed and are grouped by growth characteristics. Each of these groups represents one or more species. Although many of the isolates are from sterile sites, clinical information is often limited, and the pathogenic role of these organisms is uncertain. Some of the CDC groups of gram-negative rods or coccobacillary organisms include the following:

1. CDC group NO-1 (NO for nonoxidizer) consists of at least 22 strains of fastidious gram-negative bacilli isolated from human wounds, most of which were related to dog or cat bites.[292,293] These organisms are similar to asaccharolytic strains of *Acinetobacter* but have a negative *Acinetobacter* transformation assay, have different cellular fatty acid profiles, and, unlike

most *Acinetobacter* organisms, reduce nitrate. They are susceptible to many antimicrobial agents, including β-lactams, aminoglycosides, fluoroquinolones, and tetracycline.

2. CDC group WO-1 (WO for weak oxidizer) includes 96 oxidase-positive, motile gram-negative rods, most of which were isolated from clinical specimens.[294] One third of the clinical isolates were from blood, and 10% were from cerebrospinal fluid.[294] Signs of sepsis were present in some of the patients, but the clinical significance of this group of organisms remains unclear.
3. CDC group WO-2 isolates now reside in the genus *Pandoraea,* which has five named and at least three unnamed species. These organisms can colonize the airways of patients with cystic fibrosis and rarely can cause clinical disease, including bacteremia.[295–297] *Pandoraea* species are often resistant to ampicillin, extended-spectrum cephalosporins, and aminoglycosides and are variably susceptible to fluoroquinolones.[296]
4. CDC groups O-1, O-2, and O-3 (O for oxidizer) are phenotypically similar; they are oxidase-positive, curved gram-negative rods that do not grow on MacConkey agar but grow on *Campylobacter*-selective media. One case of group O-1 pneumonia complicated by bronchopulmonary fistula and bacteremia has been reported.[298] One group O-3 isolate that was submitted to the CDC had been identified as a *Campylobacter* species, indicating the potential for misidentification of the O-3 group.[299] The CDC collection of group O-3 includes isolates from a variety of clinical sources, including blood, lymph nodes, joint fluid, bone, and lung. They were resistant to most β-lactam antibiotics, except imipenem; all were susceptible to aminoglycosides and trimethoprim-sulfamethoxazole but not ciprofloxacin.
5. Fifteen strains of an oxidase-positive, gram-negative rod biochemically resembling *Neisseria weaveri* (CDC group M-5) are currently designated Gilardi rod group 1 by the CDC.[300] Most of the strains were isolated from human wounds of the extremities or blood cultures.

Gardnerella and *Mobiluncus* Species

Gardnerella vaginalis is difficult to characterize in terms of its microbiologic designation and its clinical relevance. By 16S rRNA sequence analysis, it is sufficiently distinct to merit its own genus but is somewhat closely related to *Bifidobacterium* species, which are anaerobic gram-positive rods.[301] It is a facultatively anaerobic, oxidase- and catalase-negative, nonsporing, nonencapsulated, nonmotile, pleomorphic, gram-variable rod (see the excellent review by Catlin.[302]) *G. vaginalis* has a thin cell wall, which does not retain the crystal violet/iodine complex on decolorization, accounting for the gram-variable or gram-negative appearance of the organism. However, the preponderance of evidence suggests that *G. vaginalis* has a gram-positive heritage.

The natural habitat for *G. vaginalis* is the human vagina, where culture-independent methods have shown that it is essentially universally present in women without signs or symptoms of vaginal infection.[303] During the development of bacterial vaginosis, the normal vaginal microbiota composition changes. Bacterial vaginosis is characterized by a decrease in numbers of lactobacilli and a predominance of *G. vaginalis* and a mixture of other anaerobic bacteria (see Chapter 108).[304] *G. vaginalis* strains associated with bacterial vaginosis have been shown to produce a cytolysin and are efficient biofilm producers.[305] However, the role of *G. vaginalis* and other organisms in the pathogenesis of bacterial vaginosis remains unclear. Molecular analyses of the vaginal microbiota of women with this disorder have discovered novel species of unculturable bacteria; some of these bacterial species are highly specific for bacterial vaginosis.[306]

Extravaginal infections caused by *G. vaginalis* are uncommon. Bacteremia is seen almost exclusively in women and is usually associated with postpartum endometritis, postpartum fever, chorioamnionitis, septic abortion, or infection after cesarean section.[307] It is a relatively infrequent urinary tract isolate, and its clinical significance can be difficult to ascertain. However, it has been recovered from suprapubic bladder aspirates from pregnant women.[308] Rare osteoarticular infections have been reported in women with or without joint prostheses and no concurrent genital infection.[309] *G. vaginalis* has also been recovered from the male urogenital tract, but definitive evidence of sexual transmission is lacking.[310] It has occasionally been associated with disease in men, often in association with urologic procedures or underlying urologic problems; reported infections include bacteremia, balanitis, urethritis, urinary tract infections, and an unusual case of urosepsis and septicemia with infective endocarditis and septic emboli.[302,311] Oral metronidazole, intravaginal metronidazole gel, or intravaginal clindamycin cream is the recommended treatment for bacterial vaginosis.[312] The utility of these agents may reflect the importance of the mixed anaerobic microbiota in bacterial vaginosis. Treatment of the sexual partner has not been shown to influence a woman's response to therapy or relapse rate, and the routine treatment of sexual partners is not recommended.[312] β-Lactams have been used to treat extravaginal infections caused by *G. vaginalis.*

Mobiluncus species are slowly growing, curved, gram-variable, motile, anaerobic bacteria predominantly found in the human vagina and also have been associated with bacterial vaginosis. *Mobiluncus* has been isolated from the vagina of as many as 97% of women with bacterial vaginosis[313] but in a minority of healthy controls.[314] However, the role of *Mobiluncus* in the pathogenesis of bacterial vaginosis is unclear. *Mobiluncus* species, more commonly *Mobiluncus curtisii,* have been associated with upper genitourinary tract infections and adverse pregnancy outcome.

Extra–genitourinary tract infections have included nonpuerperal breast abscesses, umbilical and mastectomy wounds, and a polymicrobial hepatic abscess.[315] There are several reported cases of *Mobiluncus* bacteremia, including one in a previously healthy woman who developed septic shock with coagulopathy, acute respiratory distress syndrome, and renal failure.[316] There is a single case report of a man with *Mobiluncus* bacteremia and underlying ulcerative colitis.[317] *Mobiluncus* species are usually susceptible to penicillins, ampicillin, cefoxitin, clindamycin, erythromycin, imipenem, and vancomycin,[318] but can be resistant to metronidazole.

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The complete reference list is available online at Expert Consult.

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