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Methylobacterium Species: An Increasingly Important Opportunistic Pathogen

ABSTRACT Methylobacterium *species rarely cause human disease. Those isolated from humans are usually found as opportunistic pathogens in patients weakened by an underlying disease process. This report describes a case of* Methylobacterium *bacteremia in a 35-year-old woman with AIDS, compares the clinical presentation of this case with that of other previously reported cases of* Methylobacterium *infection, and provides a history of the* Methylobacterium *genus and its relevant taxonomy. Recommendations for presumptive identification include pink to orange colony growth on blood or Sabouraud agar but not on MacConkey agar; gram-negative, vacuolated bacillus or coccobacillus; growth at 25° to 30°C and not at 42°C; and positive results on tests for oxidase and urease. Antibiotics with demonstrated efficacy against* Methylobacterium *species include amikacin, gentamicin, ciprofloxacin, trimethoprim-sulfamethoxazole, ceftizoxime, and ceftriaxone.*

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Methylobacterium species infrequently infect humans. When this does occur, the pathogens primarily cause infection in patients with severe underlying disease or immunocompromised patients.[1,2] To our knowledge, only 27 cases of *Methylobacterium* infection in humans have been reported, including the case reported here (Table 1). Underlying diseases and circumstances reported in these patients include the following:

- AIDS (three patients)[1–3]
- Lymphoma[4]
- Tuberculosis[1]
- Renal failure[1]
- Malignant neoplasms of the lung, urinary bladder, and uterus[1]
- Leukemia after bone marrow transplantation[1]
- Infusion of contaminated autologous bone marrow[5]
- Immunocompetence[6]
- Multiple sclerosis[7]
- Alcoholism[8]

We report on one of our two AIDS patients with *Methylobacterium* bacteremia. We describe the history of the genus *Methylobacterium* and review previously reported human cases of *Methylobacterium* infection to clarify the organism's classification and to develop an algorithm for the proper identification and treatment of infection with this opportunistic pathogen.

Case Report

A 35-year-old woman with AIDS came to Temple University Hospital in Philadelphia reporting a 2-day history of dehydration. The patient had been HIV-positive for 2 years, and AIDS had been diagnosed 3 months before admission on the basis of an episode of *Pneumocystis carinii* pneumonia accompanied by oral candidiasis, anal herpes, and a peripheral blood CD4 count of 38 cells/μL (0.038×10^9/L).

Physical examination revealed a thin woman with dry, cracked, scaly skin, thinning scalp hair, and patchy alopecia. She was febrile (body temperature, 101.4°F) and showed mild orthostasis. Bilateral retinal cotton-wool spots, oral thrush, and diffuse cervical, axillary, and inguinal lymphadenopathy were noted. Laboratory evaluation done at admission revealed leukopenia, anemia, thrombocytopenia, and an elevated serum creatinine level. Urinalysis was negative for evidence of infection and proteinuria, as demonstrated by negative dip stick nitrate and leukocyte esterase test results. The initial chest roentgenogram was within normal limits.

The patient was extensively evaluated for the source of the fever. Blood, urine, and sputum cultures were done, and special stains were performed on sputum for *P carinii*. Antibiotic

Table 1. Reported Cases of Human *Methylobacterium* Infection

Case No.	Age (y)/Sex	Underlying Disease	Clinical Manifestations	Site(s) of Isolation	Reference Citation
1	14/M	Tuberculous lymphadenitis, sarcoidosis	Fever, uveitis, pulmonary infiltrates, lymphadenopathy, hepatosplenomegaly	Blood, lymph node, bone marrow	1
2	1/M	Positive tuberculin test	Fever, pulmonary infiltrates, hepatosplenomegaly	Blood, liver, bone marrow	1
3	38/F	Tuberculous pneumonia	Weight loss, fever, abdominal pain, hepatomegaly, pulmonary infiltrates	Liver, lung, bone marrow, spleen, central nervous system	1
4	48/F	Uterine carcinoma	Chronic skin ulcers	Skin	1
5	38/M	Lung adenocarcinoma	Fever, pneumonia	Blood	1
6	21/M	Acute lymphoblastic leukemia, bone marrow transplant, neutropenia	Fever	Blood	1
7	18/F	Acute myelogenous leukemia, bone marrow transplant, neutropenia	Positive surveillance blood culture after antibiotic therapy	Blood	1
8	68/F	Renal failure, chronic ambulatory peritoneal dialysis	Peritonitis	Dialysate	1
9	53/M	Diabetes mellitus, chronic renal failure, peritoneal dialysis	Abdominal pain, cloudy dialysate	Dialysate	1
10	59/M	Malabsorption ("dumping syndrome") on total parenteral nutrition	Back pain, low-grade fever	Blood	1
11	41/M	AIDS, *Pneumocystis carinii* pneumonia	Fever, pulmonary infiltrates	Blood	3
12	68/M	Chronic renal failure, pneumonia	Pneumonia	Sputum	28
13	41/F	Uterine leiomyomata	Pneumonia	Sputum	28
14	80/M	Bladder tumor, liver cirrhosis	Empyema	Pleural effusion	28
15	58/M	Lung cancer (adenocarcinoma)	Pneumonia	Pleural effusion	28
16	65/M	End-stage renal disease, peritoneal dialysis	Peritonitis	Dialysate	26
17	19/M	None	Keratitis	Eye	27
18	28/F	None	Ulcer of hand	Ulcer	6
19	6/M	Acute lymphoblastic leukemia, bone marrow transplant, central line	Fever	Blood, via central line	1
20	5/F	Acute lymphoblastic leukemia, chemotherapy, central line	Dysuria, low-grade fever, erythema at catheter site	Blood	1
21	37/M	Acute myelogenous leukemia, bone marrow transplant, central line	Fever, fatigue	Blood	1
22	29/F	Wilm's tumor, bone marrow transplant	None	Blood	5
23	46/M	Multiple sclerosis	Fever, multiple urinary tract infections	Blood	7
24	35/M	AIDS	Fever of unknown origin	Blood	2
25	5/M	T-cell lymphoma	Fever, neutropenia	Blood, bone marrow	4
26	40/M	Alcoholism	Left hip pain	Synovium (left hip)	8
27	35/F	AIDS	Fever of unknown origin	Blood	Temple

Table 2. Characteristics of *Methylobacterium* Species by Laboratory Test

Test	Characteristics of *Methylobacterium* Species
Gram stain	Gram-negative (gram-variable)
Morphology	Bacilli, pleomorphic
Vacuoles	Present
Flagella	Single polar, subpolar, or lateral
Motility	Positive (often weak)
Spores	Negative
Colony morphology	Usually small
Pigment	Pink to bright red-orange
Hemolysis	Gamma
O_2 requirement	Aerobic
Utilization of 10% methanol	Positive
Growth at: 25° C	Positive
37° C	Positive
42° C	Negative
Growth on blood agar (sheep)	Positive
Growth on MacConkey agar	Negative
Oxidase	Positive
Catalase	Positive
Nitrate	Positive/negative
Urease	Positive

therapy was not started, and spontaneous defervescence occurred on the second hospital day. Fever returned that night, however, reaching 102.4°F. At this time, the initial blood cultures grew gram-positive cocci in three of four bottles. Empirical vancomycin therapy, given for 6 days, was discontinued when different organisms (*Staphylococcus epidermidis*, *Staphylococcus aureus*, and beta hemolytic *Streptococcus* group G species) were isolated from each of the positive bottles, indicating probable skin contamination.

Computed tomography of the chest and head was done to evaluate the patient for mediastinal and brain lesions, respectively, because her positive HIV reactivity (with associated leukopenia, anemia, and diffuse lymphadenopathy) raised the suspicion of lymphoma and associated fever. No mediastinal lymphadenopathy was seen, and the brain showed only mild atrophy. Bone marrow biopsy and serum protein electrophoresis yielded negative results for lymphoma and paraprotein, respectively. Collagen vascular disease was also considered because the patient had skin rash, cotton-wool spots, and eosinophilia, but results of serum studies were negative. Echocardiography showed no cardiac valvular lesions.

Intermittent fevers continued throughout the 14-day hospital course. Blood cultures obtained on the second, fourth, and eighth hospital days were negative. One of four urine cultures grew *Enterococcus* species, but this organism was considered a contaminant. A blood culture drawn on the 11th hospital day, however, was positive for a pink organism that was eventually identified as a *Methylobacterium* species and was positive for *S epidermidis*.

At discharge, the patient was prescribed maintenance therapy with trimethoprim-sulfamethoxazole. At follow-up examination 2 weeks after discharge, the patient was afebrile and reported that the fevers had resolved. The patient did not return for further evaluation.

Materials and Methods

Two blood culture bottles (BACTEC 6A and 7A, Becton Dickinson, Cockeysville, Md) were collected on the 11th hospital day. The aerobic bottle yielded positive results after 3 days, and plates demonstrated fine growth on sheep blood agar 3 days later.

No growth was seen on MacConkey agar. Two organisms were isolated: *S epidermidis* and a pink, mucoid colony. A Gram stain of the mucoid colony showed gram-negative bacilli. The mucoid colony was isolated to blood and Sabouraud agars and was analyzed with a Vitek GNI card, an API 20e, and an API/Rapid NFT (all from BioMerieux, Hazelwood, Mo). Because these systems did not definitively identify the bacterium, it was subcultured to blood agar slants and sent to the Bureau of Laboratories, Pennsylvania Department of Health, where a *Methylobacterium* species was finally identified.

Antimicrobial susceptibilities were determined by the disk diffusion method on plain Mueller-Hinton agar. The organism was sensitive to cefazolin (18 mm), ceftriaxone (28 mm), gentamicin (33 mm), tobramycin (38 mm), and trimethoprim-sulfamethoxazole (40 mm). It was resistant to ampicillin, piperacillin, cefotetan, and cefoxitin (0 mm for each drug). However, because *Methylobacterium* species are fastidious and standard disk diffusion techniques are designed for rapidly growing organisms, routine susceptibility tests may not be entirely reliable for predicting clinical outcome.

Results

The results of morphologic and biochemical testing in cases of *Methylobacterium* infection (Table 2) are consistent with an identification of *Methylobacterium* species on the basis of the phenotypic studies of Green and Bousfield and as described in *Bergey's Manual of Determinative Microbiology*.[9] The characteristics of the two most recent clinical isolates identified in the Philadelphia area are similar to the expected reactivities of previously identified *Methylobacterium* species.

A 21-day culture of the *Methylobacterium* isolate that grew from the blood of our patient is shown in Figure 1. The isolate appeared as a slowly growing, pink to coral, somewhat mucoid organism. Figure 2 is a photomicrograph of the isolate showing gram-negative, vacuolated coccobacillus, primarily arranged in chains. A photomicrograph of a Gram stain of *Vibrio extorquens* (now called *Methylobacterium extorquens*) isolated at the Centers for Disease Control and Prevention (CDC, Atlanta) in 1977 (CDC- D1912) is presented in Figure 3. This isolate was grown on heart infusion agar at 35°C for 24 hours.

Discussion

Methylobacterium species are pink, saprophytic, gram-negative bacilli that rarely cause human disease.[1,2] To our knowledge, only 27 cases of human infection have been reported. Of note, 20 of these cases have been described in the past 10 years (Table 1). Most cases have been reported in patients who are immunocompromised because of severe underlying disease or therapeutically induced immunosuppression; however, one case has been reported in an apparently immunocompetent person.[6]

Table 1, which builds on the work of Kaye and colleagues,[1] summarizes the reported cases of *Methylobacterium* infection. Several cases have been added since this review, and two cases have been excluded as a result of the most recently accepted classification. According to this system, these two cases involved other pink, gram-negative nonfermenters, not *Methylobacterium* species.[10]

The patient described in this report had bacteremia, which is the most common site of *Methylobacterium* infection (Table 1). Although the fevers may have been due to the patient's underlying HIV infection, we believe that this case represents a bona fide bacterial infection rather than contamination or colonization

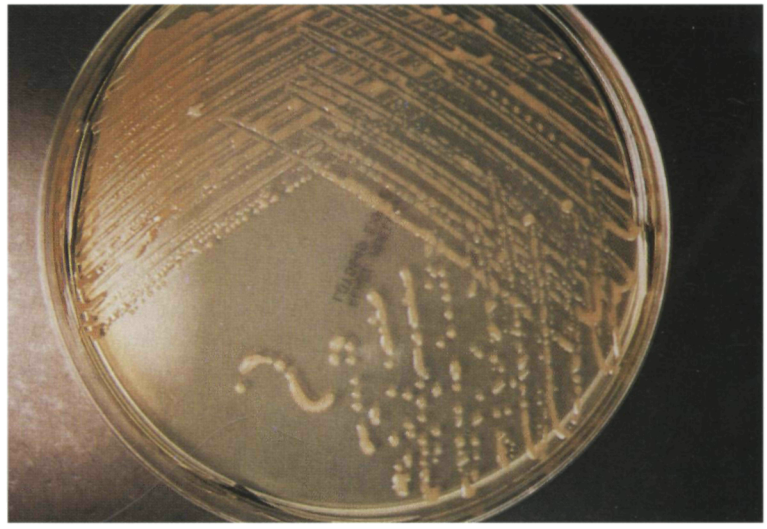

Fig 1. A 21-day culture of *Methylobacterium* species. Note the pink to coral and somewhat mucoid appearance of the colonies.

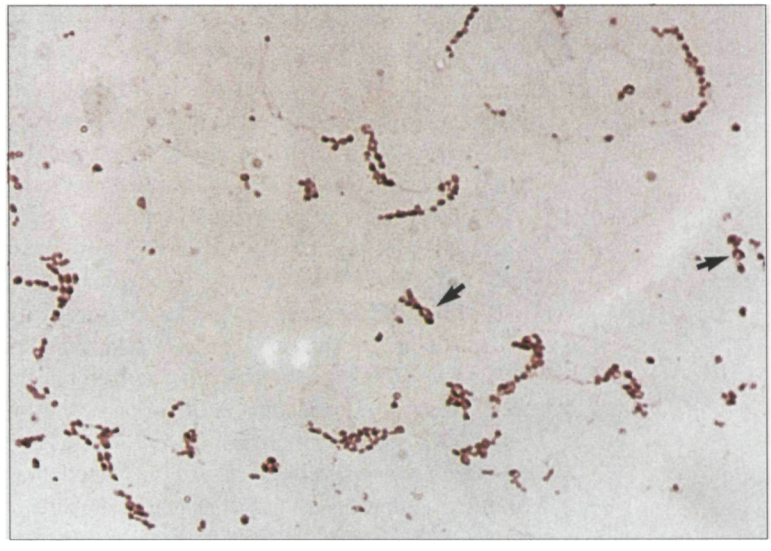

Fig 2. Gram stain of the *Methylobacterium* species isolate shown in Fig 1 (×1,000). Organisms appear primarily as bacilli, but coccobacilli and pleomorphic organisms may also be observed. Vacuoles are present (arrows).

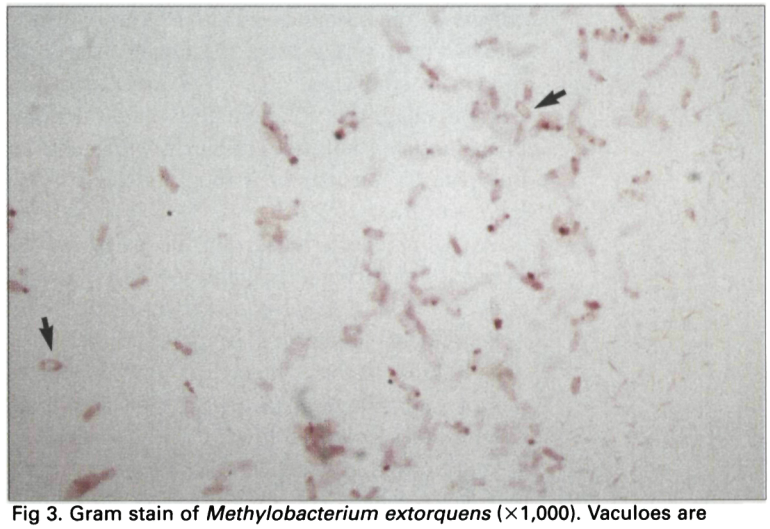

Fig 3. Gram stain of *Methylobacterium extorquens* (×1,000). Vaculoes are present (arrows). Courtesy Dr Robbin S. Weyant, Centers for Disease Control and Prevention, Atlanta

because the patient was thoroughly evaluated and no other likely source of fever was found. The growth of *S epidermidis* from the same culture bottle that harbored the *Methylobacterium* species suggests possible contamination; however, the patient's fevers did resolve after treatment with trimethoprim-sulfamethoxazole, to which the *Methylobacterium* species was sensitive in vitro. Although the portal of entry is not clear, the patient's severe seborrheic dermatitis may have compromised her skin barrier, thereby allowing entry of the organism from the external environment.

Methylobacterium species have been isolated from various sources in nature. The initial isolation may have occurred as early as 1913, from the excreta of earthworms.[11] Other sites of initial species isolation have included lake beds and the surface of a leaf.[12,13] Leaf surfaces and leaf nodules may be the primary habitat, but methylobacteria have been isolated from soil, water, air, rice grain, sewage, cow rumen, and hospitals.[12,13]

Methylobacteria have been found in both untreated and treated tap water;[14,15] they resist iodophor disinfectants, survive chlorination because they produce a glutathione-utilizing hydrolytic dechlorinating enzyme, and bind to PVC pipes.[15,16] These characteristics may explain the findings of Flournoy and colleagues, who reported a pseudo-outbreak of *Methylobacterium* pneumonia in which the source of the bacteria was found to be the tap water in a bronchoscopy suite.[17]

A 1986 report from a pediatric hospital describes three bone marrow recipients who developed nosocomial methylobacterial infections (two from blood, one from a surveillance culture of the nasopharynx) as a result of contaminated tap water used to irrigate disrupted mucous membranes.[18] The two cases identified from blood cultures (cases 6 and 7) are described in Table 1 (this table does not include the pseudo-outbreak or the patient with a positive surveillance culture).

A recent report has further identified *Methylobacterium* species and other water bacteria, such as *Pseudomonas*, *Legionella*, *Sphyngomonas*, and *Acinetobacter* organisms, in dental unit water lines.[19] Pink bacteria identified as *Methylobacterium mesophilicum* constituted 19% of all bacterial isolates found in the dental unit water lines described in this study. The investigators noted that water collected at the output of dental unit water lines is densely populated with microorganisms. This has led to some concern in the dental community because this water source has been used during invasive dental procedures. The presence of a dechlorinating enzyme in *Methylobacterium* species helps to elucidate the observation that pigmented bacteria may be more chlorine tolerant than nonpigmented forms.[19]

The genus *Methylobacterium* currently includes eight species: *M extorquens*, *Methylobacterium fujisawaense*, *M mesophilicum*, *Methylobacterium organophilum*, *Methylobacterium radiotolerans*, *Methylobacterium rhodinum*, *Methylobacterium rhodesianum*, and *Methylobacterium zatmanii*.[9,20] This classification is based on structure, biochemical characteristics, and DNA homology. These measures have provided the basis for the relocation of some species from other genera, including *Vibrio* and *Pseudomonas*. *Methylobacterium* species now include organisms formerly classified as *Pseudomonas mesophilica*, *Pseudomonas methanolica*, *V extorquens*, *Protomonas* species, *Protaminobacter rubra*, and *Mycoplasma rubra*. *Pseudomonas extorquens*, *V extorquens*, and *Flavobacterium extorquens* are now synonymous with *M extorquens*.[11,21] The genus *Protomonas* has been abandoned.

The genus *Methylobacterium* was first proposed by Patt, Cole, and Hanson in 1976 to categorize a strain of pink, rod-shaped facultative methane oxidizers originally isolated from lake water samples in 1974.[12] The new genus differed from previously described genera and species of methane-oxidizing bacteria in its ability to use various organic substrates with carbon-carbon bonds as sources of carbon and energy. In other words, this was a facultative methylotroph that not only was capable of using compounds containing no carbon-carbon bonds (such as methane or methanol), as had the previously described methylotrophs, but could also use more complex substrates with carbon-carbon bonds, such as sugars and organic acids (unlike the previously described obligate methylotrophs). The original strain was named *M organophilum* sp.nov. [ATCC27886] because of its preference for more complex organic carbon and energy sources.[12]

Two of the reference strains of the organism were later found to have lost the ability to use methane. This led Bousfield and Green to propose amending the definition to exclude methane use as an absolute requirement for membership in the genus.[22] In their studies, the grouping did have other distinctive morphologic and biochemical characteristics that appeared to justify its retention as a separate genus but that were shared

by several previously described and new bacterial strains. Thus, these researchers proposed the addition of several facultatively methylotrophic, pink, polarly flagellated, gram-negative organisms,[22] including *Pseudomonas rhodos*, renamed *M rhodinum* (Heumann, 1962); *Pseudomonas mesophilica*, renamed *M mesophilicum* (Austin and Goodfellow, 1979); and *Pseudomonas radiora*, renamed *M radiotolerans* (Ito and Iizuka, 1971).[13,22]

Methylobacteria can be differentiated from other pink bacilli, including the otherwise "unnamed taxon" of Gilardi and Faur, the CDC pink coccoid groups I through IV, and members of the *Roseomonas* genus.[23] These organisms are similar, not only in their colony and cellular structure and color but also in their ability to grow well on Sabouraud agar.[10] Whether the precise identification and differentiation of the methylobacteria from other pink, gram-negative bacilli will prove clinically and practically useful is not clear because many of these other bacteria have been reported to cause similar infections in similar patients and to have similar antibiotic sensitivity profiles.[10]

Currently available commercial bacterial identification systems do not include *Methylobacterium* species in their databases, and species-specific identification of these organisms is based on complex tests, such as cellular fatty-acid composition and "best fit" algorithms, rather than commonly available microbiological tests. From a practical standpoint, a presumptive identification is important because a final identification may take weeks or months and because the often slow growth of these organisms makes obtaining precise antibiotic sensitivities difficult. A presumptive identification aids the clinician in starting appropriate empiric antibiotic therapy while definitive identification and sensitivity testing are being performed.

Organisms that are pink-orange, gram-negative, and glucose-nonfermenting bacilli or coccobacilli and that grow on blood, Sabouraud, charcoal, or Thayer-Martin agar but not on MacConkey agar should be subcultured at incubation temperatures of 25°C, 30°C, and 42°C. Methylobacteria grow best at temperatures between 25° and 30°C and do not grow at 42°C; this temperature growth profile differentiates these organisms from other pink coccoid groups, such as *Roseomonas* species, and other pigmented organisms, such as *Chryseomonas* species. The Gram stain should always be carefully examined for vacuoles, particularly Gram stains from subcultures of the organism, where they may be more readily visible. Vacuoles are usually present in methylobacteria but are absent in morphologically similar, pigmented organisms. A wet mount should demonstrate weak bacterial motility.

In a reference laboratory, definitive identification can be shown by the organism's ability to use methane, methanol, or acetate as the sole carbon source in mineral-based media without growth factors; however, the absence of this ability does not exclude *Methylobacterium* species. Determination of fatty-acid composition may be helpful in identification. Ascertainment of a species is based on assimilation patterns of various substrates, as outlined in *Bergey's Manual of Determinative Bacteriology*.[9] In the future, taxonomic classification of this interesting group of opportunistic pathogens,[24] now defined by biochemical and chemical characteristics, will be aided by cellular fatty-acid composition and molecular hybridization studies.

Methylobacterium infections have been treated with both intravenous and oral antibiotics. Brown and colleagues[25] have used in vitro susceptibility testing with three reference strains and 15 clinical isolates of *Methylobacterium* species. Amikacin and gentamicin inhibited growth of 100% of the strains at the lowest concentrations tested. Ciprofloxacin was almost as effective in vitro, and trimethoprim-sulfamethoxazole, ceftizoxime, and ceftriaxone inhibited 100% of the isolates, although at higher concentrations. The penicillins and cephalosporins tested did not inhibit growth of any isolate. Some of the *Methylobacterium* strains tested produced beta-lactamases, but even strains that did not produce beta-lactamases were not necessarily inhibited by beta-lactam antibiotics. Beta-lactamase–resistant antibiotics were also not completely effective against the beta-lactamase producers; this finding suggests that methylobacteria have alternate mechanisms of resistance to beta-lactam agents. Amikacin or gentamicin may be used as empiric therapy for serious *Methylobacterium* infection. This therapy should be started as soon as a presumptive identification is made because the slow-growing nature of the organism may delay the determination of in vitro antimicrobial sensitivities.

Ceftizoxime, ceftriaxone, ciprofloxacin, and trimethoprim-sulfamethoxazole are also good alternate drugs.[23] In a case of peritoneal dialysis–related peritonitis for which gentamicin was ineffective, chloramphenicol eradicated the infec-

tion, presumably because of good tissue penetration. Thus, chloramphenicol may be a good alternative therapy, absent catheter removal, in a patient undergoing peritoneal dialysis who does not respond to gentamicin.[26] Minocycline was effective in a case of cutaneous *Methylobacterium* infection,[6] and topical piperacillin has been effective in the treatment of *Methylobacterium* keratitis[27,28] not responsive to topical gentamicin, tobramycin, or chloramphenicol therapy.

Conclusion

It is debated whether *Methylobacterium* species are emerging pathogens or, as postulated by some, are simply an unusual microbiological curiosity. However, our recent experience with two unrelated cases at separate hospitals in Philadelphia, as well as the experiences of others, suggests that clinical laboratories are more likely to isolate *Methylobacterium* species as opportunistic pathogens; this could be especially true as advances in medicine lead to longer lives in immunocompromised patients.

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