

Facklamia Species as an Underrecognized Pathogen

Elham Rahmati,¹ Vanessa Martin,² Darren Wong,¹ Fred Sattler,¹ Jonas Petterson,³ Pamela Ward,² Susan M. Butler-Wu,² and Rosemary C. She²

¹Department of Medicine, Division of Infectious Diseases and ²Department of Pathology, ³Keck Medical Center of the University of Southern California, Los Angeles

Facklamia species are a rarely reported etiology of clinical infection with few cases described in literature. However, the prevalence of infection may be underestimated due to challenges in species identification. We describe 3 cases of *Facklamia* species bacteremia and the unique microbiologic aspects inherent to this genus that make it particularly challenging to identify. In addition, given the unique susceptibility profile of *Facklamia* species, we discuss the importance of fully identifying this organism when it is suspected as a pathogen, to optimize therapy based on its distinct antibiotic resistance profile.

Keywords. bloodstream infection; *Facklamia*; 16S rRNA sequencing; susceptibility.

Facklamia species are Gram-positive, α -hemolytic, catalase-negative, facultative anaerobic cocci that remain challenging to accurately identify with current microbiologic identification systems. We describe 3 cases of *Facklamia* spp bacteremia to illustrate the pitfalls in laboratory identification of this genus.

CASE ONE

A 64-year-old homeless male with history of active intravenous drug use was found unresponsive in a nearby street surrounded by needles. On admission, he was hypothermic with leukocytosis of 21 K/ μ L. Two of 2 blood culture sets isolated Gram-positive cocci in chains after 72 hours. Colonies were pinpoint, sticky, pyrrolidonyl arylamidase (PYR)-negative, and α -hemolytic with no zone around A- or P-disks and with better growth in ambient air than 5% CO₂. The organism was initially reported as viridans group *Streptococcus* (VGS). Susceptibility by E-test per manufacturer's recommendations for VGS (AB Biodisk, Solna, Sweden) was read at 48 hours due

to poor growth. The pattern was unusual with elevated minimal inhibitory concentrations (MICs) to cefotaxime (32 μ g/mL) and penicillin (4 μ g/mL), later confirmed by broth microdilution method at a reference laboratory (Table 1). Matrix-assisted laser desorption ionization-time-of-flight (MALDI-TOF) mass spectrometry (Vitek MS; bioMerieux, Durham, NC) yielded no identification. Transthoracic echocardiogram and subsequent cardiac magnetic resonance imaging demonstrated an extensive 5.3 \times 3.8 \times 2.2-cm left atrial mass involving the anterior mitral valve leaflet. He was a high-risk surgical candidate and managed medically. With limited microbiologic data, the patient was treated with 6-weeks of vancomycin and gentamicin similar to treatment for penicillin-resistant enterococci. Sequencing of the first 500 base pairs of the 16S recombinant ribonucleic acid (rRNA) gene was performed, which yielded an identification of *Facklamia ignava* (99.2% identity to American Type Culture Collection [ATCC] 700631 with 4 ambiguous base pairs) [1]. The patient remained clinically stable after 6 months but refused further cardiac imaging as recommended.

CASE TWO

A 36-year-old male was admitted for suicide attempt with overdose on antidepressants. He developed acute respiratory distress syndrome from aspiration pneumonia after an observed seizure requiring intubation. Blood cultures were drawn 2 weeks after admission for fever and leukocytosis. One of 2 sets became positive after 3 days for Gram-positive cocci in chains for which he was treated with vancomycin. Colonies were pinpoint after 24 hours, non-hemolytic, and PYR-negative. The MALDI-TOF mass spectrometry identified the isolate as *Abiotrophia defectiva* (95% confidence). However, the organism displayed better growth on sheep blood than chocolate agar, a finding atypical for *Abiotrophia* species. 16S rRNA gene sequencing performed at a reference laboratory revealed the true organism identity as *Facklamia languida*. Broth microdilution susceptibility testing showed elevated MICs to cefepime, ceftriaxone, and ertapenem (Table 1). Transthoracic echocardiogram revealed no evidence of valvular vegetation. Two subsequent blood cultures were negative. The patient expired from respiratory failure 4 weeks after admission.

CASE THREE

A 59-year-old female with diabetes, chronic kidney disease requiring hemodialysis, and nonalcoholic cirrhosis with refractory ascites was admitted with abdominal pain. She denied fevers or chills. Blood cultures at the time of admission were positive after 2 days, isolating *Staphylococcus aureus*, *Peptostreptococcus anaerobius*, and a Gram-positive coccus in chains. The latter grew

Received 17 October 2016; editorial decision 20 December 2016; accepted 30 December 2016.
Correspondence: E. Rahmati, MD, 2020 Zonal Avenue, Los Angeles, CA 90033 (elham.rahmati@med.usc.edu).

Open Forum Infectious Diseases®

© The Author 2017. Published by Oxford University Press on behalf of Infectious Diseases Society of America. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (<http://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact journals.permissions@oup.com
DOI: 10.1093/ofid/ofw272

Table 1. MIC ($\mu\text{g/mL}$) of the Three *Facklamia* spp Cases Based on Broth Microdilution Method^a

Antibiotics	Case 1 <i>Facklamia ignava</i>	Case 2 <i>Facklamia languida</i>	Case 3 <i>F languida</i>
Penicillin	1 (I)	0.06 (S)	0.06 (S)
Ceftriaxone	>2 (R)	>2 (R)	>2 (R)
Cefepime	2 (I)	4 (R)	2 (I)
Vancomycin	≤ 0.5 (S)	≤ 0.5 (S)	≤ 0.5 (S)
Ertapenem	≤ 0.5 (S)	4 (NS)	4 (NS)
Levofloxacin	>4 (R)	≤ 0.5 (S)	4 (I)
Erythromycin	≤ 0.25 (S)	0.5 (I)	>2 (R)
Daptomycin	0.12 (S)	0.25 (S)	0.12 (S)

Abbreviations: I, intermediate; MIC, minimal inhibitory concentrations; NS, nonsusceptible; R, resistant; S, susceptible.

^aInterpretations given in parentheses are based on standard guidelines for viridans group streptococci [14].

in 1 aerobic bottle of 3 sets and was PYR-positive, pinpoint, and non-hemolytic on sheep blood agar. It could not be identified biochemically (RapID Strep; Remel, Lexington, KY) and was referred for 16S rRNA gene sequencing and broth microdilution susceptibility testing. It was identified as *F languida* remarkable for an elevated MIC to ceftriaxone (Table 1). Abdominal fluid cultures also grew *S aureus*. The patient was initially treated with vancomycin, cefepime, and metronidazole. Her antibiotic regimen was further narrowed to oxacillin targeting only *S aureus*. Subsequent blood cultures obtained 2 days and 3 weeks later were negative. However, due to continued clinical deterioration and a repeat abdominal fluid culture again growing *S aureus*, she was empirically treated with linezolid and ceftriaxone. The patient had a prolonged hospital course, was deemed ineligible for liver transplantation, and eventually expired from cardiorespiratory failure.

DISCUSSION

The genus *Facklamia* was first described in 1997 using 16S rRNA sequencing and has since been identified from both a wide range of animal sources and infrequently as a human pathogen [2–4]. Bacteremia has been associated with endocarditis, necrotizing gangrene, chorioamnionitis, and central nervous system disease [5–9]. Only 2 cases of possible *F ignava* infection have been reported [10], and we add a case in which it was a likely contributor to a case of endocarditis.

Although *Facklamia* spp have been implicated in invasive infections, the virulence of this organism has not been fully determined. The true extent of morbidity and mortality is further convoluted not only by the relative scarcity of reported cases, but also by the co-occurrence of *Facklamia* with other bacteria and often in patients with significant comorbidities. In addition to blood cultures, *Facklamia* has been isolated from vaginal specimens, urine, cerebrospinal fluid, bone, skin, and gall bladder [11, 12]. Because the majority of collected specimens have been from women, it has been speculated that this organism may be normal flora in the female genital tract [11, 12]. However, based on our case series, we are unable to

exclude the possibility that *Facklamia* may have originated from other sources such as the gastrointestinal tract or skin.

Similar to other uncommon *Streptococcus*-like organisms that may be isolated from clinical specimens, such as *Dolosigranulum*, *Inavigranum*, or *Vagococcus* spp, the clinical significance of *Facklamia* spp is not well understood. Although it is conceivable that all 3 of our cases of *Facklamia* isolated from blood were true pathogens, we cannot establish with absolute certainty that this organism significantly contributed to the clinical outcome of our patients. This is particularly challenging in cases 2 and 3 because *Facklamia* was only isolated from 1 set of blood cultures, which could be interpreted as contamination. On the other hand, our first case demonstrated multiple positive blood culture sets for *Facklamia* in the setting of endocarditis, which compels us to believe that *Facklamia* does have pathogenic potential.

Facklamia species are easily misidentified by traditional laboratory methods [13]. In contrast, organisms have been erroneously identified as *Facklamia* only to be later identified as *Enterococcus faecalis*, *Cardiobacterium valvarum*, or *Streptococcus mutans* by 16S rRNA gene sequencing [1]. *Facklamia* spp are similar to VGS in Gram stain, colony morphology, and catalase reaction. However, *Facklamia* spp are usually PYR-positive [10, 13], although in 2 of our cases this was not true. In each case, *Facklamia* spp grew fastidiously, requiring at least 2–3 days for blood culture bottles to flag positive. With the v2.0 Knowledge Base, the Vitek MS was unable to provide identification for *F ignava* and misidentified *F languida* as *A defectiva*. *Facklamia* spp are also not currently claimed in the Bruker Biotyper MALDI-TOF system. This underscores the continuing need for bench microbiologist expertise in spite of advances in technology. With limited experience in *Facklamia* identification for most laboratories, it appears at the current time that definitive identification is best made by deoxyribonucleic acid sequence analysis.

It is important to distinguish *Facklamia* spp from VGS and *Streptococcus*-like organisms because of its unusual susceptibility profile. Limited antimicrobial susceptibility studies have shown *F ignava* and *F languida* isolates to possess elevated MICs to cefotaxime, erythromycin, clindamycin, and trimethoprim-sulfamethoxazole and low MICs to levofloxacin and vancomycin. *Facklamia ignava*, but not *F languida*, may have elevated penicillin MICs. For *F languida*, elevated carbapenem MICs have also been observed [12]. Recognition of the susceptibility profiles for *Facklamia* spp could help in raising suspicion if the organisms were misidentified, eg, as VGS or *Abiotrophia* spp cases of *Facklamia* spp bacteremia with associated necrotizing gangrene, chorioamnionitis, and central nervous system disease were previously treated effectively with vancomycin, amoxicillin/clavulanic acid, and ceftriaxone plus vancomycin, respectively [5, 7, 9]. Endocarditis due to *Facklamia* spp has only been described in 2 cases of *Facklamia hominis* where 1 case was treated successfully with ceftriaxone and gentamicin [6] and 1 case resulted in fatal myocardial infarction despite 2

days of vancomycin and gentamicin [8]. Because there are no guidelines for treatment of *Facklamia* spp bacteremia, clinical decisions must be made based on data from nonstandardized susceptibility testing; empiric treatment with vancomycin would be appropriate given the variable susceptibility profiles of *Facklamia* to β -lactam drugs. Based on limited published clinical experience and our own case, for *Facklamia* endocarditis, treatment with 6 weeks of β -lactam antibiotic or vancomycin with 2 weeks of gentamicin may be a reasonable choice.

CONCLUSIONS

Facklamia spp are organisms whose true virulence and pathogenesis are poorly understood. They may cause infection in a susceptible host, but clarifying the risk factors has proven to be difficult based on the scarcity of literature. Due to challenges in its identification, the true burden of disease may be under-recognized. However, the importance of appropriate identification should not be discounted because susceptibilities for *Facklamia* may differ significantly from the VGS for which it may be misidentified. This potential resistance to β -lactams may have significant clinical treatment implications.

Acknowledgment

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Petti CA, Polage CR, Schreckenberger P. The role of 16S rRNA gene sequencing in identification of microorganisms misidentified by conventional methods. *J Clin Microbiol* **2005**; 43:6123–5.
2. Collins MD, Falsen E, Lemozy J, et al. Phenotypic and phylogenetic characterization of some *Globicatella*-like organisms from human sources: description of *Facklamia hominis* gen. nov., sp. nov. *Int J Syst Bacteriol* **1997**; 47:880–2.
3. Hoyles L, Foster G, Falsen E, et al. *Facklamia miroungae* sp. nov., from a juvenile southern elephant seal (*Mirounga leonina*). *Int J Syst Evol Microbiol* **2001**; 51:1401–3.
4. Takamatsu D, Ide H, Osaki M, Sekizaki T. Identification of *Facklamia sourekii* from a lactating cow. *J Vet Med Sci* **2006**; 68:1225–7.
5. Pérez Alonso AJ, Husein-El Ahmed H, Del Olmo Rivas C, et al. *Facklamia sourekii* necrotizing gangrene. *Med Mal Infect* **2012**; 42:283–4.
6. Ananthkrishna R, Shankarappa RK, Jagadeesan N, et al. Infective endocarditis: a rare organism in an uncommon setting. *Case Rep Infect Dis* **2012**; 2012:307852.
7. Healy B, Beukenholt RW, Tuthill D, Ribeiro CD. *Facklamia hominis* causing chorioamnionitis and puerperal bacteraemia. *J Infect* **2005**; 50:353–5.
8. Safavi S, Tufnell M, Bhalla A. Multi-territory ischaemic strokes and subacute bacterial endocarditis. *BMJ Case Rep* **2010**; 2010(pii):bcr0620092023.
9. McCann E, Barber M, Hunter P, Inverarity D. A very unusual organism causing stroke-like symptoms. *Age Ageing* **2014**; 43:727–8.
10. Collins MD, Lawson PA, Monasterio R, et al. *Facklamia ignava* sp. nov., isolated from human clinical specimens. *J Clin Microbiol* **1998**; 36:2146–8.
11. Parvataneni KC, Iyer S, Khatib R, Saravolatz LD. *Facklamia* species and *Streptococcus pneumoniae* meningitis: a case report and review of the literature. *Open Forum Infect Dis* **2015**; 2:ofv029.
12. LaClaire L, Facklam R. Antimicrobial susceptibilities and clinical sources of *Facklamia* species. *Antimicrob Agents Chemother* **2000**; 44:2130–2.
13. LaClaire LL, Facklam RR. Comparison of three commercial rapid identification systems for the unusual Gram-positive cocci *Dolosigranulum pigrum*, *Ignavigranum ruoffiae*, and *Facklamia* species. *J Clin Microbiol* **2000**; 38:2037–42.
14. CLSI. *Performance Standards for Antimicrobial Susceptibility Testing*. 26th ed. CLSI supplement M100S. Wayne, PA; Clinical and Laboratory Standards Institute; **2016**.