A Case of Wound Infection with *Providencia rettgeri* and Coincident Gout in a Patient from Guam

Michael A. Washington PhD; Jason Barnhill PhD; and Jaclyn M. Griffin NP

Abstract

Providencia rettgeri (P. rettgeri) *is a ubiquitous organism that is infrequently associated with human disease. Here we report the isolation of this organism from a polymicrobial wound infection resulting from ruptured tophi on a 54-year-old male patient from Guam. We describe the identification and confirmation of this organism, and propose metabolic synergy as a possible mechanism of pathogenesis. To our knowledge, this is the first published report of a wound infection colonized by P. rettgeri from Guam, and the first report to speculate upon the role of bacterial synergy in P. rettgeri pathogenesis.*

Providencia rettgeri (*P. rettgeri*) is a motile, gram-negative rod shaped organism and a member of the *Enterobacteriaceae* family.[1] It is capable of growth on MacConkey agar, capable of catalyzing the dissociation of urea into ammonia and carbon dioxide, capable of deaminating phenylalanine, and capable of producing gas from glucose fermentation. However, most strains are incapable of fermenting lactose, a defining feature of the genus *Providencia*.[2] The first members of this genus were isolated by Leo F. Rettger of the Sheffield Laboratory at Yale University. These isolations were undertaken as part of an epidemiological investigation into a 1904 fowl cholera epidemic.[3] However, the organisms were not characterized until about 1918 when Phillip Hadley performed a cursory evaluation of the genus and proposed the name *Bacterium rettgeri* to refer to an unusual urease producing strain. In 1943, Rustigian and Stuart recommended that *Bacterium rettgeri* be assigned to the genus *Proteus* based on biochemical characteristics.[3] However, a series of DNA-DNA hybridization studies by Brenner and others in 1978 demonstrated a clear relationship between certain members of the genus *Proteus* and certain members of the genus *Providencia*. This recognition resulted in the reassignment of *Proteus rettgeri* to the genus *Providencia*.[3]

The first report of a human infection with *P. rettgeri* was published in 1951. This report, by Goldfarb and De Bakey, described a case of *P. rettgeri*-associated empyema.[4] Antibiotic resistant strains of this organism were reported as early as 1971. These reports were initiated by Traub, Craddock, and others who reported an outbreak of a lactose fermenting, highly antibiotic resistant strain of *P. rettgeri* among surgical ward patients.[5] A second large outbreak of *P. rettgeri* (urinary tract infection) was reported by Edwards, and others, in 1974.[6] Furthermore, this organism had been implicated in the etiology of gastrointestinal illness in 1986, traveler's diarrhea in 2004, and ocular infection in 2006.[7-9] It is of interest to note that *P. rettgeri* has been identified as the causative agent of "purple bag syndrome," an unusual and striking condition in which purple-tinted urine is produced as a result of bacterial enzymatic activity.[10] A 2014 report on the isolation of *P. rettgeri* from a cluster of surgical infections in Nepal illustrates the presence and significance of this organism in the Asia-Pacific region.[11] With regard to antimicrobial susceptibility, *P. rettgeri* is typically resistant to gentamicin and tobramycin but susceptible to amikacin. There have been reports of extended spectrum beta lactamase (ESBL) producing *P. rettgeri* in Eastern Europe and New Delhi, and metallo-beta lactamase (NDM-1) producing *P. rettgeri* isolates in South America and Asia.[11-15]

We describe a case of an ampicillin-resistant *P. rettgeri* wound infection coincident with tophaceous gout in a polymicrobial wound on a patient from Guam. This is the first published report of this organism in association with gouty tophi. This report may represent a sentinel case that indicates the presence of an antibiotic-resistant, human-colonizing strain of *P. rettgeri* circulating in the Marianas and it may represent the first indication of this organism participating in a synergistic relationship with other bacterial species colonizing a wound site.

Case Report

A 54-year-old man from Guam with no significant travel history, no indication of insect bites, or immunosuppression, and a medical history significant for hypertension, chronic kidney disease, and tophaceous gout was referred to our facility due to the presence of multiple wounds resulting from ruptured tophi, and worsening symptoms. Upon presentation, the wounds were found on the left shin. A punch biopsy was performed and samples were sent to the laboratory for histological analysis and bacterial culture. Histology was negative for neoplasm and bacterial isolate analyses utilizing the Vitek 2 (bioMerieux, Hazelwood MO) phenotypic identification system revealed the presence of 2+ *Staphylococcus aureus* (*S. aureus*), 2+ *Pseudomonas aeruginosa (P. aeruginosa)*, and 2+ *P. rettgeri*.[16] Due to the fact that *P. rettgeri* is an unusual cause of wound infection, the identity of this isolate was confirmed by matrix-assisted desorption/ionization time of flight mass spectrometry using the Vitek MS (mass spectrometry) system.[17]

Sensitivity studies revealed that the isolate was resistant to ampicillin, ampicillin/sulbactam, cefazolin, gentamicin, and trimethoprim/sulfamethoxazole. It was found to be susceptible to ceftriaxone, cefepime, ciprofloxacin, and piperacillin/tazobactam. The patient was initially treated with clindaymycin (300mg QID x 10 days) and ciprofloxacin (500mg BID x 10 days) to cover both gram negative and gram positive pathogens as the *Pseudomonas* isolate was susceptible to ciprofloxacin and the *Staphylococcus* isolate was susceptible to clindamycin. Local wound care was initiated with topical polymem silver foam. This treatment was continued daily. At 10 days post-

presentation, creatinine levels were elevated to 2.09 mg/dl and potassium levels were elevated to 5.7 mEq/L. The patient also complained of diarrhea. He was therefore advised to stop both ciprofloxacin and clindamycin therapy. Topical treatments with polymem silver foam were continued. At this time, his wounds were greatly improved and without signs of active infection. At a two week follow-up, the initial wounds were in a state of resolution and repeat cultures were positive only for an antibiotic sensitive strain of *Pseudomonas aeruginosa* and *Corynebacterium* species (most likely representing a skin contaminant). These results suggest that the abbreviated antibiotic therapy in combination with the topical application of polymem silver foam was effective in eliminating both *Providencia* and *Staphylococcus* infections and that it was sufficient to initiate the process of wound resolution.

Discussion

Wound infections with *P. rettgeri* are rarely reported in the literature. To date, there has been no confirmed association between *P. rettgeri* and topheaceous gout. A PubMed search using the Boolean search terms "wound" and "*Providencia rettgeri*" yielded only seven results.[18] Three of those were in reference to the flora recovered from snakes and snake bites, one was in reference to horse wounds, two were a study of the attraction of certain insects to volatile compounds released from wound infections, and one was a study on catheter-associated urinary tract infections.[19-25] In contrast, a search using the Boolean search terms "wound" AND "*Staphylococcus*" yielded 7,375 results, the majority of which were directly related to skin and soft tissue infection.[26]

The fact that *P. rettgeri* is not often associated with wound infection is rather surprising given that this is an organism with an almost ubiquitous presence in the environment. It has been isolated from such diverse locations as fresh water sources, run-off wastewater, and explosive-contaminated soil.[27,28] In addition, this organism has been found living as either a commensal or a pathogen in several invertebrate and vertebrate species including the fruit fly (*Drosophila melanogaster*), the Black Cobra (*Naja naja karachiensis*), the snake *Bothrops jararaca*, and several species of waterfowl, horses, and alligators.[19-22,30-32] Interestingly, screwworm flies (*Calliphoridae*) appear to be attracted to organic compounds generated by fresh cultures of *P. rettgeri* indicating that mechanical vector transmission may be possible.[23,24]

In the present case, it is unclear where the organism was acquired. However, it is significant that the patient had a history of tophaceous gout and presented in the clinic with multiple ruptured tophi. Superinfection of gouty tophi is a well-known complication of the condition and it is one of the most common reasons for surgical intervention.[33] It is possible that *P. rettgeri* was inoculated into ruptured tophi during water or soil exposure. It is also possible that prior colonization with *Pseudomonas* and *Staphylococcus* set the stage for *P. rettgeri* superinfection by triggering local attenuation of the immune response and by initiating the formation of a protective biofilm. However, given that the pathophysiology of gout involves the accumulation of uric acid crystals at the site of tophi formation, the fact that *P. aeruginosa* produces urate oxidase, which initiates the hydrolysis of uric acid to urea and the fact that *P. rettgeri* is capable of the hydrolysis of urea to ammonia and carbon dioxide, it is tempting to speculate that the colonization of a site with multiple tophi was the result of a urea-based chemotactic response initiated by the degradation of uric acid by *P. aeruginosa*.[34-36] Indeed, certain strains of *Helicobacter pylori* have shown both a urease dependent and a urease independent chemotactic response to urea.[36-38]

If the local decomposition of uric acid to urea initiated by *P. aeruginosa* was sufficient to drive secondary colonization by *P. rettgeri*, the decomposition of urea to ammonia by this organism may have been partially responsible for the tissue damage at the wound site. Indeed, scenarios in which pathogenesis is augmented by metabolic synergy has been described for several oral pathogens and such a scenario would explain the initiation of wound resolution following the antibiotic-mediated elimination of *P. rettgeri*.[39,40] However, further studies will be required to determine whether *P. aeruginosa* and *P. rettgeri* synergize *in vivo*, whether this activity increases pathogenesis and whether this activity is accelerated in cases of gout.

The contribution of *P. rettgeri* to the pathology of wound infection has yet to be determined. It is often difficult to differentiate between those organisms that merely colonize a wound site and those organisms that are truly pathogenic.[41] No definitive virulence factors have been described for *P. rettgeri*. Nonetheless, there is mounting evidence to suggest that, under certain conditions, urease can act as a general virulence factor.[42] The reported toxicity of bacteria-produced ammonia to epithelial cells supports the notion of wound-site pathology catalyzed by bacterial urea and uric acid degradation.[42,43] This hypothesis is especially attractive with respect to the present case, given the role of uric acid in the pathology of gout, the ability of *P. aeruginosa* to decompose uric acid, and the ability of *P. rettgeri* to convert the resulting end products to ammonia. A 2001 report by Murray and Comearu describes a case of hyperammonemia resulting from a *P. rettgeri* infection.[434] This case was so severe that the patient suffered a coma that only resolved with the elimination of *P. rettgeri* by antibiotic therapy.[36] This report clearly demonstrates that the urease activity of *P. rettgeri* is significant, and that it is capable of altering clinical outcomes.

Conclusion

Although *P. rettgeri* is rarely reported as the sole cause of wound infection, the isolation of this organism from a wound site should not be summarily dismissed. *P. rettgeri* maintains two traits that may serve to aggravate tissue injury. These are the possession of antimicrobial resistance mechanisms and the ability to produce ammonia from urea. Either of these traits can potentially influence the ecology of the wound site and alter the kinetics of wound healing. In the present case, antibiotic therapy appeared to eliminate both the *P. rettgeri* infection and the *S. aureus* infection and elimination of these two organisms

appeared to correlate with the initiation of wound resolution. Despite the fact that *P. rettgeri* is a known producer of ammonia, it is impossible to determine the extent to which this organism contributed to overall wound pathology. A greater understanding of the pathophysiology of *P. rettgeri* (including the role of metabolic synergy as a mechanism of virulence) will be required to develop the means to reliably discriminate between cases of colonization versus cases of infection, to identify and eliminate bacterial synergy, and to facilitate the development of proper treatment guidelines.

The views expressed in this manuscript are those of the authors and do not reflect the official policy or position of the Department of the Army, Department of Defense, or the US government.

Conflict of Interest

None of the authors identify a conflict of interest.

Authors' Affiliation:
- Tripler Army Medical Center; Honolulu, HI

Correspondence to:
Michael A. Washington PhD; Tripler Army Medical Center, 1 Jarrett White Rd., Honolulu, HI 96859; E-mail: michael.a.washington120.mil@mail.mil

References

1. Manos J, Belas R. The genera Proteus, Providencia, and Morganella. In: *The Prokaryotes*. New York, NY: Springer; 2006:585-606.
2. Farmer JJ, Hickman FW, Brenner DJ, Schreiber M, Rickenbach, DG. Unusual Enterobacteriaceae. Proteus rettgeri that change into Providencia stuartii. *Journal of Clinical Microbiology*. 1977;6:373-378.
3. O'Hara CM, Brenner FW, Miller, JM. Classification, identification, and clinical significance of Proteus, Providencia, and Morganella. *Clinical Microbiology Reviews.* 2000;13:534-546.
4. Goldfarb, PM., De Bakey E. Empyema due to Proteus rettgeri, report of a case with recovery. *Journal of the Medical Association of the State of Alabama.* 1951;21:33-37.
5. Traub WH, Craddock ME, Raymond EA, Fox, M, McCall. Characterization of an unusual strain of Proteus rettgeri associated with an outbreak of nosocomial urinary-tract infection. *Applied Microbiology*. 1971;22:278-283.
6. Edwards LD, Cross A, Levin S, Landau W. Outbreak of a nosocomial infection with a strain of Proteus rettgeri resistant to many antimicrobials. *American Journal of Clinical Pathology*. 1974;61:41–46.
7. Müller HE. Occurrence and pathogenic role of Morganella-Proteus-Providencia group bacteria in human feces. *Journal of Clinical Microbiology*. 1986;23:404-405.
8. Yoh M, Matsuyama J, Ohnishi M, et al. Importance of Providencia species as a major cause of travelers' diarrhea. *Journal of Medical Microbiology.* 2005;54:1077-1082.
9. Koreishi AF, Schechter BA, Karp CL. Ocular infections caused by Providencia rettgeri. *Ophthalmology*. 2006;113:1463-1466.
10. Al-Jubouri M, Vardhan, M. A case of purple urine bag syndrome associated with Providencia rettgeri. *Journal of Clinical Pathology.* 2001;54:412.
11. Tada T, Miyoshi-Akiyama T, Dahal RK, et al. NDM-1 Metallo-beta-Lactamase and ArmA 16S rRNA methylase producing Providencia rettgeri clinical isolates in Nepal. *BMC Infectious Diseases.* 2014;14:56.
12. Marchandin H, Carriere C, Sirot D, Jean-Pierre H, Darbas H. TEM-24 Produced by Four Different Species of Enterobacteriaceae, Including Providencia rettgeri, in a Single Patient. *Antimicrobial Agents and Chemotherapy.* 1999;43:2069-2073.
13. Cornaglia G, Frugoni S, Mazzariol A, Piacentini E, Berlusconi A, Fontana R. Activities of oral antibiotics on Providencia strains isolated from institutionalized elderly patients with urinary tract infections. *Antimicrobial Agents and Chemotherapy.* 1995;39:2819-2821.
14. Barrios H, Garza-Ramos U, Reyna-Flores F, et al. Isolation of carbapenem-resistant NDM-1-positive Providencia rettgeri in Mexico. *Journal of Antimicrobial Chemotherapy.* 2013;68:1934-1936.
15. Carvalho-Assef APDA, Pereira PS, Albano RM, et al. Isolation of NDM-producing Providencia rettgeri in Brazil. *Journal of Antimicrobial Chemotherapy.* 2013;68:2956-2957.
16. Ling TK, Tam PC, Liu ZK, Cheng AF. Evaluation of VITEK 2 rapid identification and susceptibility testing system against gram-negative clinical isolates. *Journal of Clinical Microbiology.* 2001;39:2964-2966.
17. Martiny D, Busson L, Wybo I, El Haj RA, Dediste A, Vandenberg O. Comparison of the MICROFLEX LT and VITEK® MS systems for the routine identification of bacteria by Matrix-Assisted Laser Desorption-Ionization Time-Of-Flight Mass Spectrometry. *Journal of Clinical Microbiology*. 2012;50:1313-1325.
18. US National Library of Medicine: National Institutes of Health Web site. http://www.ncbi.nlm.nih.gov/pubmed/?term=wound+AND+%22providencia+rettgeri%22. Accessed June 5, 2015.
19. Iqbal J, Sagheer M, Tabassum N, Siddiqui R, Khan NA. Culturable Aerobic and Facultative Anaerobic Intestinal Bacterial Flora of Black Cobra (Naja naja karachiensis) in Southern Pakistan. ISRN Veterinary Science [serial online]. April 2014; 878479. doi: 10.1155/2014/878479.
20. Jorge MT, Ribeiro LA, Da Silva MLR, Kusano EJU, de Mendonça JS. Microbiological studies of abscesses complicating Bothrops snakebite in humans: a prospective study. *Toxicon.* 1994;32:743-748.
21. Jorge MT, Mendonça JSD, Ribeiro LA, Silva MLRD, Kusano EJU, Cordeiro CLDS. Bacterial flora of the oral cavity, fangs and venom of Bothrops jararaca: possible source of infection at the local bite. *Revista do Instituto de Medicina Tropical de São Paulo.* 1990;32:6-10.
22. Cochrane CA, Freeman K, Woods E, Welsby S, Percival SL. Biofilm evidence and the microbial diversity of horse wounds. *Canadian Journal of Microbiology.* 2009;55:197-202.
23. Chaudhury MF, Skoda SR, Sagel A, Welch JB. Volatiles emitted from eight wound-isolated bacteria differentially attract gravid screwworms (Diptera: Calliphoridae) to oviposit. *Journal of Medical Entomology.* 2010;47:349-354.
24. Hammack L. Oviposition by screwworm flies (Diptera: Calliphoridae) on contact with host fluids. *Journal of Economic Entomology.* 1991;84:185-190.
25. Dedeić-Ljubović A, Hukić, M. Catheter-related urinary tract infection in patients suffering from spinal cord injuries. *Boston Journal of Basic Medical Science.* 2009;9:2-9.
26. US National Library of Medicine: National Institutes of Health Web site. http://www.ncbi.nlm.nih.gov/pubmed/?term=wound+AND+%22staphylococcus%22. Accessed June 5, 2015.
27. Kitts CL, Cunningham DP, Unkefer PJ. Isolation of three hexahydro-1, 3, 5-trinitro-1, 3, 5-triazine-degrading species of the family Enterobacteriaceae from nitramine explosive-contaminated soil. *Applied and Environmental Microbiology.* 1994;60:4608-4611.
28. Abo-Amer AE, Ramadan AB, Abo-State M, Abu-Gharbia MA, Ahmed HE. Biosorption of aluminum, cobalt, and copper ions by Providencia rettgeri isolated from wastewater. *Journal of Basic Microbiology.* 2013;53:477-488.
29. Juneja P, Lazzaro BP. Providencia sneebia sp. nov. and Providencia burhodogranariea sp. nov., isolated from wild Drosophila melanogaster. *International Journal of Systematic and Evolutionary Microbiology*. 2009;59:1108-1111.
30. Cheong CY, Lee CK, Zuki Z. A rare infection following snakebite. *Malaysian Orthopaedic Journal.* 2010;4:53-55.
31. Aguirre AA, Cook RS, McLean RG, Quan TJ, Spraker TR. Occurrence of potential pathogens in wild Caribbean flamingos (Phoenicopterus ruber ruber) during a lead poisoning die off in Yucatan, Mexico. *Journal of Zoo and Wildlife Medicine.* 1991;22:470-475.
32. Camus AC, Hawke JP. Providencia rettgeri-associated septicemia and meningoencephalitis in juvenile farmed American alligators Alligator mississippiensis. *Journal of Aquatic Animal Health*. 2002;14:149-153.
33. Choi HK, Mount DB, Reginato AM. Pathogenesis of gout. *Annals of internal medicine*. 2005;143:499-516.
34. Campbell LL. Oxidative degradation of uric acid by cell extracts of a Pseudomonas. *Biochimica et Biophysica Acta.* 1955;18:160-161.
35. Bachrach U. The aerobic breakdown of uric acid by certain pseudomonads. *Journal of General Microbiology*. 1957;17:1-11.
36. Magana-Plaza I, Ruiz-Herrera J. Mechanisms of regulation of urease biosynthesis in Proteus rettgeri. *Journal of Bacteriology*. 1967;93:1294-1301.
37. Mizote T, Yoshiyama H, Nakazawa T. Urease-independent chemotactic responses of Helicobacter pylori to urea, urease inhibitors, and sodium bicarbonate. *Infection and Immunity*. 1997;65:1519-1521.
38. Nakamura H, Yoshiyama H, Takeuchi H Mizote T, Okita K, Nakazawa T. Urease plays an important role in the chemotactic motility of Helicobacter pylori in a viscous environment. *Infection and Immunity*. 1998;66:4832-4837.
39. Tan KH., Seers CA, Dashper SG, et al. Porphyromonas gingivalis and Treponema denticola exhibit metabolic symbioses. *PLoS Pathogens.* 2014;10:e1003955.
40. Orth RH, O'Brien-Simpson NM, Dashper SG, Reynolds EC. Synergistic virulence of Porphyromonas gingivalis and Treponema denticola in a murine periodontitis model. *Molecular Oral Microbiology*. 2011;26:229-240.
41. Dani A. Colonization and infection. *Central European Journal of Urology*. 2014;67:86.
42. Rutherford JC. The emerging role of urease as a general microbial virulence factor. *Plos Pathogens.* 2014;10(5):e1004062. doi: 10.1371/journal.ppat.1004062. eCollection 2014.
43. Mégraud F, Neman-Simha V, Brügmann D. Further evidence of the toxic effect of ammonia produced by Helicobacter pylori urease on human epithelial cells. *Infection and Immunity*. 1992;60:1858-1863.
44. Murray T, Leonard L. Comeau. Hyperammonemic coma caused by Providencia rettgeri infection in a child with prune belly syndrome. *Pediatric Critical Care Medicine*. 2001;2:178-180.