Trimethoprim/Sulfamethoxazole and Moxifloxacin Therapy for a Pediatric *Stenotrophomonas Maltophilia* Ventriculoperitoneal Shunt Infection

Eric R. Gregory, PharmD; Sam B. Osborne, PharmD; Brian M. Gardner, PharmD; and Robert A. Broughton, MD

Stenotrophomonas maltophilia is an increasingly prevalent cause of nosocomial infections. This report describes a 5-month-old male diagnosed with a *S maltophilia* ventriculoperitoneal shunt infection after a neurosurgical procedure. Intravenous trimethoprim/sulfamethoxazole and moxifloxacin successfully treated the patient. A literature review revealed a scarcity of similar reports, with none using moxifloxacin as an effective concomitant treatment with trimethoprim-sulfamethoxazole.

ABBREVIATIONS TMP/SMZ, trimethoprim/sulfamethoxazole; VP, ventriculoperitoneal

KEYWORDS moxifloxacin; pediatric; *Stenotrophomonas maltophilia*; ventriculoperitoneal shunt

J Pediatr Pharmacol Ther 2019;24(1):61–65

DOI: 10.5863/1551-6776-24.1.61

Introduction

Stenotrophomonas maltophilia (*S maltophilia*) is the third most commonly isolated non-fermenting aerobic Gram-negative bacillus, behind *Pseudomonas aeruginosa* and *Acinetobacter baumannii*.^{1,2} Although this ubiquitous motile bacterium can be found in numerous settings, its nosocomial incidence is increasing in the United States.² The most common infections reported are ventilator-associated pneumonia and bacteremia, with risk factors being immunosuppression, indwelling devices such as endotracheal tubes or ventriculoperitoneal (VP) shunts, and prior antimicrobial therapy.² Of the pediatric central nervous system infections caused by *S maltophilia* reported in the literature, we present the first known case using moxifloxacin and trimethoprim/sulfamethoxazole (TMP/SMZ) combination therapy.

Case

A 5-month-old Caucasian male with a past medical history of birth at 37 weeks' gestation, early onset *Streptococcus agalactiae* sepsis without meningitis, and bilateral grade 3 intraventricular hemorrhages complicated by hydrocephalus requiring placement of a functioning right occipital ventriculoperitoneal (VP) shunt 3 months after birth was referred from an outside facility to our institution. The patient's chief complaints included a 5-day history of intermittent irritability, a history of poor weight gain since birth due to prior complications, and more recently, weight loss of 1.8 kg over a period of 4 days regardless of formula supplementation.

On admission, the 5.6-kg patient exhibited no mental status change from baseline according to the mother,

but serum leukocytosis of 29,600/ μ L (6000–13,300/ μ L) and thrombocytosis of 825,000/ μ L (244,000–580,000/ μ L) were present (Table). Magnetic resonance imaging of the head suggested worsened hydrocephalus. While an infectious workup was underway, the patient was afebrile until his temperature rose to 38°C on hospital day 3. A urinalysis was normal, and a blood culture collected was negative for growth. By hospital day 3, the primary team ruled out non-infectious causes and considered other possibilities. The neurosurgery service performed a shunt tap at the reservoir on hospital day 4 and results were consistent with bacterial meningitis. The cerebrospinal fluid (CSF) revealed white blood cell (WBC) count 1770/ μ L (0–30/ μ L) with 79% neutrophils, 4% lymphocytes, and 11% monocytes; red blood cell (RBC) count 1000/ μ L; glucose of 18 mg/dL (60–80 mg/dL); protein > 600 mg/dL (15–45 mg/dL); and a negative Gram stain. Given the concern for potential progression toward ventriculitis, he was started on empiric therapy of vancomycin 80 mg/kg/day divided every 6 hours and cefepime 150 mg/kg/day divided every 8 hours, pending culture results. Initially, all bacterial, acid fast, and fungal cultures were negative. Abdominal ultrasonography revealed a small amount of ascites but no fluid collection around the end of the shunt. On hospital day 6, the shunt was externalized and CSF from the distal end of the shunt revealed WBC > 10,000/ μ L, RBC 2667/ μ L, and numerous Gram-negative rods on Gram stain, which resulted as *S maltophilia* upon culturing.

While awaiting antimicrobial susceptibility results, he was started on intravenous TMP/SMZ 18 mg/kg/day, based on the TMP component, divided every 8 hours, cefepime was changed to ceftazidime 150 mg/kg/day divided every 8 hours, and vancomycin was discontinued. The following day, susceptibility test-

Results	Day 1	Day 4	Day 6	Day 8	Day 10	Day 11
Serum (per μ L)						
WBC (nl: 6000–13,300)	29,600	27,300	24,500			
Platelets (nl: 244,000–580,000)	825,000	898,000	935,000			
CSF						
WBC (nl: 0–30/ μ L)	1770		>10,000	489		145
Neutrophils, per μ L	1398.30		>8900	190.6		5.8
Lymphocytes, per μ L	70.8		>100	122.3		88.4
Glucose (nl: 60–80 mg/dL)	18		<2	27		26
Protein (nl: 15–45 mg/dL)	>600		>600	>600		>600
Cultures						
Blood		NGTD				
CSF		NGTD	<i>S maltophilia</i>	<i>S maltophilia</i>		NGTD
CSF Gram stain		None	Numerous GNRs	Moderate GNRs		No organisms
Antimicrobial therapy		FEP, VAN	FEP, VAN, MTZ	VAN, CAZ, TMP/SMZ	TMP/SMZ, MXF	TMP/SMZ, MXF
Surgical interventions		VP shunt tap	VP shunt externalization	VP shunt sent for analysis	VP shunt removed; EVD placement	Analysis of VP shunt tip

CAF, cefazidime; EVD, external ventricular drain; FEP, cefepime; GNRs, Gram-negative rods; MTZ, metronidazole; nl, normal; MXF, moxifloxacin; NGTD, no growth to date; TMP/SMZ, trimethoprim/sulfamethoxazole; VAN, vancomycin; VP, ventriculoperitoneal; WBC, White Blood Cells

ing of his isolate revealed susceptibility to TMP/SMZ (minimum inhibitory concentration [MIC] 0.094 mg/L) and levofloxacin (MIC 0.75 mg/L), but resistance to ceftazidime (MIC > 256 mg/L). Due to the severity of the infection, the bacteriostatic activity of TMP/SMZ, concern for potential development of resistance to TMP/SMZ monotherapy, and evidence from the literature suggesting that a combination of TMP/SMZ with a fluoroquinolone may demonstrate *in vitro* synergy against some strains of *S maltophilia*, it was recommended by the pediatric infectious diseases service to add intravenous moxifloxacin 10 mg/kg/day.

Although the shunt was externalized on hospital day 6, it was removed in its entirety on hospital day 9 and an external ventricular drain was subsequently placed on the same day. CSF sent from the end of the removed shunt at the time of surgery also grew *S maltophilia*. However, CSF cultures obtained from the external ventricular drain on postoperation days 2, 4, 7, and 9 after removal of the shunt and initiation of combination therapy with TMP/SMZ and moxifloxacin were negative. He improved clinically with resolution of fever and irritability, his leukocytosis resolved, and he began to gain weight as his metabolic demands decreased with treatment of his infection. His shunt was eventually replaced, and he received a total of 21 days of targeted combination therapy for a *S maltophilia* VP shunt infection before being discharged from the hospital. As of 6 months from discharge, the patient's growth and mental capacity were progressing well, and there were no reports of relapse or concern for VP shunt failure.

Discussion

TMP/SMZ is considered the drug of choice against *S maltophilia* infections; however, a review of previous literature suggests other agents have been initiated empirically as combination therapy for serious infections in select patients.^{3,4} To our knowledge, this is the first case to report use of TMP/SMZ in combination with moxifloxacin to treat a *S maltophilia* VP shunt infection in a pediatric patient.

TMP/SMZ monotherapy has been shown to provide bacteriostatic activity in an *in vitro* pharmacodynamic model.⁵ An evaluation of TMP/SMZ alone and in combination with other antibiotics was reported over a 48-hour period in 4 susceptible *S maltophilia* isolates by Zelenitsky et al.⁵ Combination therapy was defined as clinical adult doses equivalent to TMP/SMZ 5 to 25 mg/kg every 12 hours with one of the following: ceftazidime 2000 mg every 12 hours, gentamicin or tobramycin 2.5 mg/kg every 12 hours, or ciprofloxacin 400 mg every 12 hours.⁵ When compared with the growth control, TMP/SMZ alone did not decrease the bacterial count against any isolate tested. On the other hand, antibiotic combinations exhibited a significant killing effect, with bacterial colony count reductions

ranging from 1.3 to 4.0 log₁₀ at 24 hours and from 0.6 to 2.2 log₁₀ at 48 hours. The analysis results indicated TMP/SMZ in combination with an additional agent was associated with an increased killing effect compared with TMP/SMZ monotherapy. Therefore, combination therapy against *S maltophilia* should be considered for serious infections requiring bactericidal activity as in this patient case.

Because Zelenitsky et al⁵ observed a beneficial effect *in vitro* when using an antibiotic combination versus TMP/SMZ monotherapy, a decision was needed to determine the second agent for the care of the patient. To further compare the efficacy of individual fluoroquinolones, a direct evaluation of moxifloxacin and ciprofloxacin against *S maltophilia* isolates was performed by Ba et al.⁶ In the pharmacodynamic assessment of ciprofloxacin 750 mg orally every 12 hours versus moxifloxacin 400 mg orally every 24 hours against fluoroquinolone-susceptible *S maltophilia* strains, moxifloxacin resulted in more robust killing. Analysis of 3 different *in vitro* strains showed moxifloxacin to have a greater killing effect at 12 hours by $\Delta \log \text{CFU/mL}$ with an increased area under the curve (AUC)₀₋₂₄/MIC and AUC₂₄₋₄₈/MIC.⁶ Although other fluoroquinolones are available for treatment, moxifloxacin was chosen for this patient case in part due to its consistently greater activity than ciprofloxacin against the isolates in this *in vitro* study.

Evidence from a time-kill study reinforced the idea of a moxifloxacin and TMP/SMZ combination as an option. Clinical isolates of *S maltophilia* were analyzed against TMP/SMZ, minocycline, tigecycline, moxifloxacin, and ceftazidime for efficacy and susceptibility when used alone and in combination.⁷ Of the 12 strains included in the study, 4 were susceptible to moxifloxacin, 2 of which were TMP/SMZ-susceptible and 2 were TMP/SMZ-resistant. Although all monotherapy regimens exhibited bacteriostatic activity, the combination of TMP/SMZ and moxifloxacin resulted in bactericidal activity in all 4 moxifloxacin-susceptible strains, including those resistant to TMP/SMZ monotherapy.⁷ When evaluating *S maltophilia* resistance patterns, clinicians may consider a combination of TMP/SMZ and moxifloxacin for bactericidal activity in isolates displaying resistance to TMP/SMZ but susceptibility to moxifloxacin.

S maltophilia, as a multidrug resistant non-fermenting Gram-negative bacilli, requires pharmacodynamic targets of AUC₀₋₂₄/MIC > 100 and C_{max}/MIC of 8 to 10 to achieve effective activity when treated with fluoroquinolones.⁸ Therefore, an aggressive dosing schedule was used in the reported case to account for pharmacokinetic and pharmacodynamic factors. Intravenous moxifloxacin 10 mg/kg/day was chosen using a previous study evaluating the pharmacokinetics of HIV-infected children being treated for multidrug resistant tuberculosis, which also requires similar pharmacodynamic targets.^{9,10} Although the study reported lower AUC and

serum moxifloxacin concentrations in children based on oral 10 mg/kg/day doses compared with adults receiving 400 mg by mouth per day, the investigators suggested this was likely related to HIV-related complications, such as decreased absorption with oral medications.¹⁰ Because the case patient received moxifloxacin parenterally, 100% absorption was achieved.

The moxifloxacin and TMP/SMZ regimen was selected based on reported evidence, but the fluoroquinolone is not indicated for *S maltophilia* therapy and there remained concern for *in vitro* susceptibility against the cultured isolate. The institutional Microbiology Laboratory reported a levofloxacin MIC of 0.75 mg/L via Etest, but testing was not performed using moxifloxacin. However, a previously reported susceptibility profile indicated an excellent correlation between levofloxacin 4 mg/L and moxifloxacin 2 mg/L against *S maltophilia*, suggesting the possibility of extrapolating a levofloxacin MIC as a surrogate marker for moxifloxacin use in situations such as this case.¹¹

Moxifloxacin, along with other fluoroquinolones, is known to penetrate both the CSF and the gastrointestinal tract very well, but further data are needed to confirm this conclusion for pediatric patients.¹² Although variable, moxifloxacin is known to have the greatest AUC CSF/plasma ratio of the fluoroquinolones in adults treated for tuberculous meningitis. It can reach as high as 0.82 after a single dose of moxifloxacin 400 mg by mouth, whereas median CSF/plasma ratios have been found to be 0.74 and 0.26 for levofloxacin 500 mg by mouth every 12 hours and ciprofloxacin 750 mg by mouth every 12 hours, respectively.^{12,13} In the uninflamed to mildly inflamed meninges, moxifloxacin penetration can be as high as 0.46, similar to other fluoroquinolones.¹⁴ Therefore, central nervous system penetration is favorable and clinicians may consider using the drug for such infections.

Treatment selection for the reported case was created using previous literature. Nevertheless, concern for adverse drug events, such as musculoskeletal injury, was considered due to previously described changes in weight-bearing joint cartilage of juvenile canines after fluoroquinolone exposure.¹⁵ In humans, however, only a small number of patients with suspected fluoroquinolone-associated musculoskeletal disorders have been reported. In a 5-year follow-up study of the characteristics and severity of adverse events of fluoroquinolone exposure in pediatric patients comparing levofloxacin to amoxicillin/clavulanic acid, no difference in the incidence of clinical musculoskeletal injuries was observed in the 2 groups.¹⁵ Because the patient in this case was very young and non-weight bearing, it was felt the benefit outweighed the potential risks; no adverse effects were reported with moxifloxacin during treatment or at a 6-month follow-up visit.

In conclusion, we present a case of a *S maltophilia*

VP shunt infection effectively treated with moxifloxacin and TMP/SMZ. The case of a 5-month-old male with a *S maltophilia* central nervous system infection is the first reported to successfully and safely treat with this combination. When clinically warranted, clinicians could consider this treatment regimen in the setting of ceftazidime resistance.

ARTICLE INFORMATION

Affiliations Department of Pharmacy Services (ERG, SBO, BMG), UK HealthCare, Lexington, Kentucky; Department of Pharmacy Practice and Science (BMG), University of Kentucky College of Pharmacy, Lexington, Kentucky; Division of Infectious Diseases (RAB), Department of Internal Medicine, University of Kentucky College of Medicine, Lexington, Kentucky

Correspondence Brian M. Gardner, PharmD;
brian.gardner@uky.edu

Disclosure The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. The authors had full access to all patient information in this report and take responsibility for the integrity and accuracy of the report.

Accepted June 18, 2018

Copyright Published by the Pediatric Pharmacy Advocacy Group. All rights reserved.
For permissions, email: matthew.helms@ppag.org

REFERENCES

1. Palleroni NJ, Bradbury JF. *Stenotrophomonas*, a new bacterial genus for *Xanthomonas maltophilia* (Hugh 1980) Swings et al. 1983. *Int J Syst Bacteriol*. 1993;43(3):606–609.
2. Chang YT, Lin CY, Chen YH, Hsueh PR. Update on infections caused by *Stenotrophomonas maltophilia* with particular attention to resistance mechanisms and therapeutic options. *Front Microbiol*. 2015;6:1–20.
3. Toleman MA, Bennett PM, Bennet DM, et al. Global emergence of trimethoprim/sulfamethoxazole resistance in *Stenotrophomonas maltophilia* mediated by acquisition of *sul* genes. *Emerg Infect Dis*. 2007;13(4):559–565.
4. Falagas ME, Valkimadi PE, Huang YT, et al. Therapeutic options for *Stenotrophomonas maltophilia* infections beyond co-trimoxazole: a systematic review. *J Antimicrob Chemother*. 2008;62(5):889–894.
5. Zelenitsky SA, Iacovides H, Ariano RE, Harding GKM. Antibiotic combinations significantly more active than monotherapy in an *in vitro* infection model of *Stenotrophomonas maltophilia*. *Diagn Microbiol Infect Dis*. 2005;51(1):39–43.
6. Ba BB, Feghali H, Arpin C, et al. Activities of ciprofloxacin and moxifloxacin against *Stenotrophomonas maltophilia* and emergence of resistant mutants in an *in vitro* pharmacokinetic-pharmacodynamic model. *Antimicrob Agents Chemother*. 2004;48(3):946–953.

7. Wei C, Ni W, Cai X, et al. Evaluation of trimethoprim/sulfamethoxazole (SXT), minocycline, tigecycline, moxifloxacin, and ceftazidime alone and in combinations for SXT-susceptible and SXT-resistant *Stenotrophomonas maltophilia* by *in vitro* time-kill experiments. *PLoS ONE*. 2016;11(3):e0152132.
8. Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. *Clin Infect Dis*. 1998;26(1):1–10.
9. Shandil RK, Jayaram R, Kaur P, et al. Moxifloxacin, ofloxacin, sparflaxacin, and ciprofloxacin against *Mycobacterium tuberculosis*: evaluation of *in vitro* and pharmacodynamic indices that best predict *in vivo* efficacy. *Antimicrob Agents Chemother*. 2007;51(2):576–582.
10. Thee S, Garcia-Prats AJ, Draper HR, et al. Pharmacokinetics and safety of moxifloxacin in children with multidrug-resistant tuberculosis. *Clin Infect Dis*. 2015;60(4):549–556.
11. Gales AC, Jones RN, Sader HS. Antimicrobial susceptibility profile of contemporary clinical strains of *Stenotrophomonas maltophilia* isolates: can moxifloxacin activity be predicted by levofloxacin MIC results? *J Chemother*. 2008;20(1):38–42.
12. Alffenaar JW, van Altena R, Bokkerink HJ, et al. Pharmacokinetics of moxifloxacin in cerebrospinal fluid and plasma in patients with tuberculous meningitis. *Clin Infect Dis*. 2009;49(7):1080–1082.
13. Thwaites GE, Bhavnani SM, Chau TT, et al. Randomized pharmacokinetic and pharmacodynamic comparison of fluoroquinolones for tuberculous meningitis. *Antimicrob Agents Chemother*. 2011;55(7):3244–3253.
14. Kanellakopoulou K, Pagoulatou A, Stroumpoulis K, et al. Pharmacokinetics of moxifloxacin in non-inflamed cerebrospinal fluid of humans: implication for a bactericidal effect. *J Antimicrob Chemother*. 2008;61(6):1328–1331.
15. Bradley JS, Kauffman RE, Balis DA, et al. Assessment of musculoskeletal toxicity 5 years after therapy with levofloxacin. *Pediatrics*. 2014;134(1):146–153.