CASE REPORT

Stenotrophomonas Infection in a Patient with Glucose-6-Phosphate Dehydrogenase Deficiency

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The drug of choice for treatment of *Stenotrophomonas maltophilia* is sulfamethoxazole/trimethoprim, and second-line therapy usually consists of a fluoroquinolone. However, in patients with glucose-6-phosphate dehydrogenase deficiency, neither sulfamethoxazole/trimethoprim nor a fluoroquinolone is a preferred option as it may result in hemolysis. Currently, there is a paucity of data regarding treatment of *S maltophilia* infection in these patients. This case report presents a patient who was successfully treated with doxycycline and inhaled colistimethate.

INDEX TERMS colistimethate, doxycycline, G6PD deficiency, *Stenotrophomonas*

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INTRODUCTION

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is estimated to affect 400 million people and is the most common enzymatic defect in humans. It is more common in African, Asian, Mediterranean, and Middle Eastern countries but is increasing in number in other locations as migration occurs. The geographic rates of G6PD deficiency are similar to patterns of malaria and are thought to be protective against the tropical illness. It occurs more often in males as it is a recessive X-linked disorder.[1]

G6PD converts nicotinamide adenine dinucleotide phosphate ($NADP^+$) to its reduced form (NADPH) which is utilized to convert oxidized glutathione to its reduced form. This allows hydrogen peroxide to be converted to water, avoiding oxidative injury to cells (Figure).[2] This pathway is most vital to erythrocytes, as it is the only means by which they can produce NADPH and protect against oxidative cell injury. Thus, the most common problem in patients with G6PD deficiency is hemolytic anemia. It is usually associated with an infection or oxidative medication such as primaquine or dapsone. Other medications including sulfamethoxazole and fluoroquinolones have been associated with hemolysis in G6PD-deficient patients.

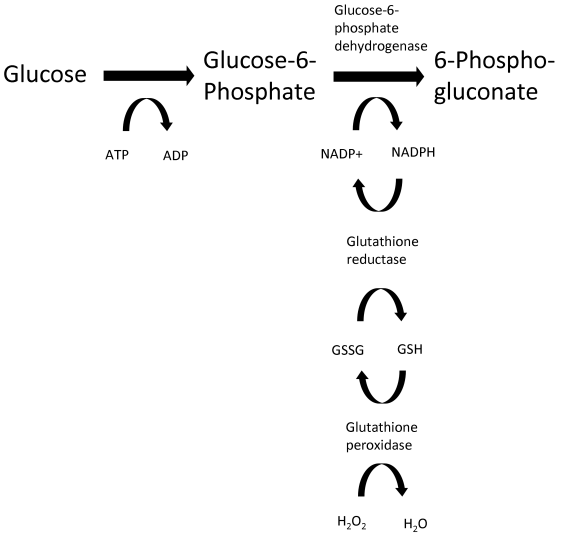

Figure. Production and Mechanism of Protection of G6PD from Oxidative Injury.
ADP, adenosine diphosphate; ATP, adenosine triphosphate; H_2O, water; H_2O_2, hydrogen peroxide; GSH, reduced glutathione; GSSG, oxidized glutathione; $NADP^+$, nicotinamide adenine dinucleotide phosphate (oxidized form); NADPH, nicotinamide adenine dinucleotide phosphate (reduced form).

Stenotrophomonas maltophilia is a Gram-negative multidrug resistant organism that is similar to *Pseudomonas* and was once referred to as *Pseu-*

Table. Patient's Tracheostomy Cultures

	Day -111	Day 0	Day 17	Day 308
Method of culture	Tracheostomy aspirate	Tracheostomy aspirate	Tracheostomy aspirate	Tracheostomy aspirate
Respiratory Culture	Many *Pseudomonas aeruginosa* x 2 colonies; Many *Serratia marcescens*	Many *Pseudomonas aeruginosa;* Many *Stenotrophomonas maltophilia*	Many *Pseudomonas Aeruginosa*	Many *Pseudomonas Aeruginosa;* Some *Enterobacter aerogenes*
Gram Stain	Some segmented neutrophils; Few epithelial cells	Many segmented neutrophils; Rare epithelial cells	Many segmented neutrophils; No epithelial cells	Many segmented neutrophils; Rare epithelial cells

domonas maltophilia. It is a waterborne organism that can be found in numerous sources in the environment, including soil, rivers, and lakes. This organism is not highly virulent and is usually associated with respiratory infections. Sulfamethoxazole and fluoroquinolones are the first-line agents used for treatment of infections by these organisms.[3] *S maltophilia* infection rates are increasing, especially, in immunocompromised patients. An associated mortality rate of up to 37.5% has been reported in the literature.[4] Antimicrobial selection is limited because of the presence of multidrug resistant efflux pumps and low membrane permeability for beta-lactams.[5]

Presented here is a patient with a history of G6PD deficiency who developed *S maltophilia* tracheitis. Currently, there is no known literature regarding treatment of *S maltophilia* infection in patients with G6PD deficiency. To our knowledge, this is the first case report of a patient with G6PD deficiency treated for *S maltophilia* tracheitis. Our experience may provide other practitioners with a possible therapy should a similar case present itself. This report was exempt from Institutional Review Board approval.

CASE REPORT

A 12-year-old African-American male patient with a history of congenital cytomegalovirus infection, microcephaly, cerebral palsy, developmental delay, seizure disorder, factor VII deficiency, tracheostomy, and G6PD deficiency was admitted to the hospital for long-term access placement. On the day of discharge, the patient began to have fever. Tracheal aspirate cultures were obtained, empirical treatment with cefdinir was started, and the patient was discharged. The white blood cell count on the previous day was 14.6 thousands per microliter. Previous cultures had shown the patient to be colonized with *Pseudomonas aeruginosa*. The new sputum culture grew *P aeruginosa* and *S maltophilia*. Despite treatment with cefdinir, the family reported the patient continued with fever and symptoms resembling respiratory distress. The outpatient clinic preferred to start the patient on oral antibiotics to avoid hospitalization. When a treatment plan was formulated, the decision was made to focus therapy on *S maltophilia* as the primary organism. The patient had multiple cultures previously positive for *P aeruginosa*, and the physician felt that it was a colonization and was not responsible for the patient's current symptoms. Because of the patient's G6PD deficiency, the standard first-line agent, sulfamethoxazole/trimethoprim, and second-line agent, a fluoroquinolone, for *S maltophilia* treatment were not options.

The patient was started on oral doxycycline, 100 mg twice daily, and nebulized colistimethate, 75 mg twice daily, for 10 days to treat the *S maltophilia* infection. The original culture was tested for response to ticarcillin/clavulanic acid as a possible alternative antibiotic. The organism was shown to be resistant to ticarcillin/clavulanic acid, and a minimum inhibitory concentration was not provided. Susceptibility to other antimicrobials was not conducted. A culture repeated 17 days after the initial culture was negative for *S maltophilia*. The patient's fever and respiratory symptoms resolved. Sputum cultures remained negative for *S maltophilia* for over 1 year (Table).

DISCUSSION

In this case report, a patient with G6PD deficiency that developed a possible *S maltophilia* tracheitis requiring therapy is presented. Upon

review of the literature, the authors were unable to find examples of a similar case. Treatment of bacterial tracheitis consists of maintenance of the airway, antimicrobial therapy, and fluid resuscitation, if necessary. Tracheitis can be a serious illness that can require hospitalization and possible intubation even in a patient without complex medical history.[6] Symptoms include fever, increased white blood cell count, and inflammation or irritation of the trachea. In this particular case, airway maintenance was already in place as the patient had had a tracheostomy. Other treatments might have included anti-inflammatory agents to decrease swelling and inflammation. However, treating tracheitis with glucocorticoids has not been found to provide additional benefit.[7] Antibiotic therapy was the important factor in this case because of the *S maltophilia* that was cultured and the patient's other disease states.

It was decided to treat this patient's *S maltophilia* organism-infected respiratory culture given his fever and respiratory distress. Bacterial tracheitis may have varied presentations and organisms.[8] Difficulty arises in therapeutic management of tracheitis, as organisms isolated from the tracheal aspirate may not be the causative organism of infection. In this case, the patient had had multiple previous positive respiratory cultures for *P aeruginosa*. *S maltophilia* was an organism newly found in this patient's tracheal aspirate. The culture had many colonies of *S maltophilia*, and the patient was clinically deteriorating. With the information available, the decision was made to treat the *S maltophilia* infection with appropriate antimicrobial therapy.

Sulfamethoxazole/trimethoprim is the drug of choice for treatment of *S maltophilia* infection. However, this drug should be avoided in patients with G6PD deficiency.[9] Fluoroquinolones may be considered second-line therapy for *S maltophilia* infections. Nalidixic acid is an older quinolone that has been shown to cause hemolytic anemia in patients with G6PD deficiency.[3] International medication guides for fluoroquinolones have a warning to avoid their use in patients with G6PD deficiency. In addition, a few cases of hemolytic anemia associated with fluoroquinolones have been reported.[10,11] Due to the lack of evidence of hemolytic anemia with the newer quinolones, some authors suggest that these agents may still be used in this patient population.[3] Because the patient was to undergo outpatient therapy, he would not be able to be monitored for hemolytic anemia associated with fluoroquinolone therapy. Therefore, it was decided to avoid using this class of medication in the outpatient setting.

Data have suggested that other treatment options can include doxycycline. Doxycycline has been shown to be an acceptable agent in vitro for third-line treatment of *S maltophilia* infection. An article by Valdezate et al[12] compared resistance rates of various antimicrobials in 99 strains of *S maltophilia* at their institution. Doxycycline had a 1% rate of resistance compared to a 27.3% rate of resistance for sulfamethoxazole/trimethoprim and an approximate resistance rate of 50% for ticarcillin/clavulanic acid. In another article comparing *S maltophilia* isolates from patients with cystic fibrosis and those without, resistance rates for doxycycline were documented at 6.4% (n=47) and 0% (n=51), respectively.[13]

Colistimethate has limited evidence for use in *S maltophilia* infections. In a recent case series, Iosifidis et al[14] reported their results with use of intravenous colistimethate in several pediatric patients. Two patients had *S maltophilia* susceptible to colistimethate. In addition to colistimethate, both patients were taking several other antibiotic therapies. Both patients survived despite the serious nature of their infections. A recent article described a patient who had previously received courses of sulfamethoxazole/trimethoprim and fluoroquinolones. The patient developed ciprofloxacin-resistant *S maltophilia*, and a course of sulfamethoxazole/trimethoprim failed. The authors proceeded to treat the *S maltophilia* infection with intravenous doxycycline and inhaled colistimethate. The patient improved clinically over the course of therapy and was eventually discharged.[15] Due to the successful treatment of this patient and the other literature reviewed, doxycycline and inhaled colistimethate were chosen.

Doxycycline is not recommended for patients younger than 8 years of age. Other therapy options would need to be pursued in those children who have G6PD deficiency and a *S maltophilia* infection. Ticarcillin/clavulanic acid may be an option in these very young patients. *S maltophilia* has been reported to be susceptible to ticarcillin/clavulanic acid in 18.6% to 55.7% of cases.[16,17] Because of these low numbers, susceptibility would need to be determined prior to recommending ticarcillin/clavulanic acid.

Sulfamethoxazole/trimethoprim remains the standard of care for treatment of *S maltophilia* infection. Patients may have other medical conditions, such as G6PD deficiency, that increase the risk of injury if this therapy is used. Having knowledge of alternative regimens is useful to the clinician. This particular regimen is beneficial because it can be used on an outpatient basis.

In this case, *S maltophilia* infection was successfully treated with doxycycline and inhaled colistimethate in a patient with G6PD deficiency. After a thorough review of the literature, no other similar cases were found. Based on the patient's age, what is known about the disease state, and other case reports of *S maltophilia* infection treatment, this therapy was chosen. We also recommended inhaled colistimethate as a duplicate therapy in an effort to eradicate the organism. The patient's cultures remained negative for *S maltophilia* after combination treatment with doxycycline and inhaled colistimethate. This case report may provide a point of reference for practitioners caring for a similar patient.

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.

ABBREVIATIONS ADP, adenosine diphosphate; ATP, adenosine triphosphate; G6PD, glucose-6-phosphate dehydrogenase; GSSG, oxidized glutathione; GSH, reduced glutathione; H_2O_2, hydrogen peroxide; H_2O, water; $NADP^+$, nicotinamide adenine dinucleotide phosphate; NADPH, reduced nicotinamide adenine dinucleotide phosphate

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REFERENCES

1. Cappellini MD, Fiorelli G. Glucose-6-phosphate dehydrogenase deficiency. *Lancet*. 2008;371(9606):64-74.
2. Frank JE. Diagnosis and management of G6PD deficiency. *Am Fam Physician* 2005;72(7):1277-1282.
3. Youngster I, Arcavi L, Schechmaster R, et al. Medications and glucose-6-phosphate dehydrogenase deficiency: an evidence-based review. *Drug Saf*. 2010;33(9):713-726.
4. Falagas ME, Kastoris AC, Vouloumanou EK, et al. Attributable mortality of *Stenotrophomonas maltophilia* infections: a systematic review of the literature. *Future Microbiol*. 2009;4(9):1103-1109.
5. Brooke JS. *Stenotrophomonas maltophilia*: an emerging global opportunistic pathogen. *Clin Microbiol Rev*. 2012;25(1):2-41.
6. Graf J, Stein F. Tracheitis in pediatric patients. *Semin Pediatr Infect Dis*. 2006;17(1):11-13.
7. Miranda AD, Valdez TA, Pereira KD. Bacterial tracheitis: a varied entity. *Pediatric Emerg Care* 2011;27(10):950-953.
8. Tebruegge M, Pantazidou A, Thorburn K, et al. Bacterial tracheitis: a multi-centre perspective. *Scand J Infect Dis*. 2009;41(8):548-557.
9. World Health Organization working Group. Glucose-6-phosphate dehydrogenase deficiency. *Bull World Health Organ*. 1989;67(6):601-611.
10. Oh YR, Carr-Lopez SM, Probasco JM, Crawley PG. Levofloxacin-induced autoimmune hemolytic anemia. *Ann Pharmacother*. 2003;37(7-8):1010-1013.
11. Sansone S, Rottensteiner J, Stocker J, et al. Ciprofloxacin-induced acute haemolytic anaemia in a patient with glucose-6-phosphate dehydrogenase Mediterranean deficiency: a case report. *Ann Hematol*. 2010;89(9):935-937.
12. Valdezate S, Vindel A, Loza E, et al. Antimicrobial susceptibilities of unique stenotrophomonas maltophilia clinical strains. *Antimicrob Agents Chemother*. 2001;45(5):1581-1584.
13. Canton R, Valdezate S, Vindel A, et al. Antimicrobial susceptibility profile of molecular typed cystic fibrosis *Stenotrophomonas maltophilia* isolates and differences with noncystic fibrosis isolates. *Pediatr Pulmonol*. 2003;35(2):99-107.
14. Iosifidis E, Antachopoulos C, Ioannidou M, et al. Colistin administration to pediatric and neonatal patients. *Eur J Pediatr*. 2010;169(7):867-874.
15. Wood GC, Underwood EL, Croce MA, et al. Treatment of recurrent stenotrophomonas maltophilia ventilator-associated pneumonias with doxycycline and aerosolized colistin. *Ann Pharmacother*. 2010;44(10):1665-1668.

16. Wu H, Wang JT, Shiau YR, et al. A multicenter surveillance of antimicrobial resistance on Stenotrophomonas maltophilia in Taiwan. *J Microbiol Immunol Infect*. 2012;45(2):120-126.

17. Sader HS, Jones RN. Antimicrobial susceptibility of uncommonly isolated non-enteric gram-negative bacilli. *Int J Antimicrob Agents*. 2005;25(2):95-109.