

Case report

Extended-Spectrum Beta-lactamases (ESBL-EC) producing *Escherichia coli* Urinary Tract Infection treated with Ozone Therapy

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Abstract

Multidrug resistant bacterial isolates have significantly increased in recent years as a cause of bacterial cystitis. This increasing resistance to antimicrobial drugs leaves fewer therapeutic options for effective treatment.

The emergence of antibiotic resistant bacteria in the community is necessitating the need to explore non-pharmacologic treatment options to reduce the spread and proliferation of these species. Ozone is an emerging therapy with both potent antibacterial properties and the ability to modulate the immune system, reduce oxidative stress induced by chronic infection and upregulate the endogenous antioxidant system providing further protection from free radical injury. In this case report, it is discussed how a patient with chronic ESBL-EC cystitis with limited therapeutic options was effectively treated with ozone therapy.

It is shown a case study of a 67-year-old female with a neurogenic bladder who developed chronic cystitis caused by ESBL-producing and multi-drug resistant *E. coli* (ESBL-EC). It was treated with bladder instillations of ozonated distilled water, combined with Major Autohemotherapy (MAHT) as an adjunctive immune modulated support.

The current findings show that the elimination of a case of chronic cystitis caused by ESBL-EC was effectively treated with an alternative to pharmacologic antimicrobial therapy utilizing distilled instillation of ozonated water and Major Autohemotherapy. Further studies are warranted to investigate this as a potential therapeutic option for this and other resistant bacterial infections.

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Background

Multidrug resistant isolates have significantly increased in recent years and have created a public health concern for the development of treatments against bacterial infections such as urinary tract infections (UTI).^{1,2} Among these isolates, there is a major concern for multi-drug resistant Enterobacteriaceae (commonly the *Escherichia coli* species) which may produce extended-spectrum β -lactamases (ESBLs).² The first isolation of ESBL in 1983 was in Germany and since then it has been increasingly reported globally.³ ESBL-producing *E. coli* (ESBL-EC) enzymes are capable of hydrolyzing penicillins, cephalosporins and monobactams.³

Carbapenems are considered the most dependable treatment for infections caused by ESBL-producing bacteria.⁴ However, since resistance has emerged, this has led to finding alternative antibiotics for UTIs so that carbapenems can be set aside for more critical infections. Alternate antimicrobials that may be used for treatment include nitrofurantoin, fosfomycin, amikacin, cefepime, and piperacillin/tazobactam.⁵

The aim of this case study is to explore an alternate form of therapy for UTI as treatment options have become limited. We report a case study of a UTI caused by ESBL-producing and multidrug resistant *E. coli* effectively treated with bladder instillations of ozonated water combined with Major Autohemotherapy as an adjunctive immune support.

Case Presentation

The patient is a 67 year old white female who presents with recurrent urinary tract infections caused by ESBL-EC. In 2012, the patient was found to have uterine prolapse and subsequent development of a neurogenic bladder. Initially, she was able to retract the bladder and urinate adequately but then eventually developed an atonic bladder and the need for self-catheterization 5 to 7 times per day. She began to have recurrent UTIs with community-acquired *E. coli*, which improved with the use of a hormonal based vaginal cream and intermittent antibiotic treatment. She was advised to take oral daily Nitrofurantoin as a prophylactic agent by the urogynecologist but she declined. Instead she was treated with intermittent antibiotics when she was symptomatic and had a positive culture. In April 2017, the patient developed urinary urgency, dysuria, fever, and malaise. A urine culture was positive for ESBL-EC and she consulted with the urogynecologist and was prescribed Nitrofurantoin for 10 days. Then in August 2017, she had a recurrence of the ESBL-EC and was prescribed Gentamicin bladder instillations daily for seven days with a follow-up culture being negative for bacterial infection.

She consulted with an infectious disease physician at the request of her urogynecologist and was told that she was a chronic carrier of this bacteria and would have the disease the rest of her life. She was advised to take daily suppressive antimicrobial therapy. She declined therapy and sought consultation at The Logan Institute for Health and Wellness for options regarding her treatment. After a thorough discussion with the patient informing her of her treatment options, as well as the potential risks, she elected to proceed with the ozone therapy consisting of Major Autohemotherapy and bladder instillations of ozonated distilled water. The initial treatment with MAHT began at a dose of 80 mL blood volume at 20 µg/mL weekly for 5 weeks but was increased as tolerated throughout the course of therapy which is shown in Table 1. Despite the negative urine culture, the MAHT was started on week 1 for generalized immune support, oxidative preconditioning and to prepare the patient for elective hysterectomy/colpopexy to try and improve bladder function and eliminate the prolapse. She had the surgery three weeks after completion of the first cycle of MAHT. Following surgery, she developed postoperative fever, elevated white blood cell count and a positive urine culture for ESBL-EC. She was treated with Macrodantin for 10 days and her symptoms resolved. She then re-consulted with the infectious disease physician and was recommended to have daily antibiotic therapy or IV therapy, again which she declined. The physician agreed with a trial of ozone therapy. She returned to the clinic for additional therapy and bladder instillations were implemented along with the MAHT at this time. The dosage of ozone in the MAHT was increased as noted below.

Table 1: Major Autohemotherapy Protocol

Timeline of Treatment	Dose
Week 1-5	80 mL at 20 µg/mL
Week 6-8*	80 mL at 30 µg/mL
Week 9-11	80 mL at 35 µg/mL
Week 12-14	80 mL at 40 µg/mL
*: 2 month hold in treatment after week 9 due to patient's surgery	

The bladder instillations consisted of ozonated distilled water that was ozonated for 10 min at 80 µg/mL (See Attachment 1 for protocol details). Then 100 mL of the ozone water was instilled using a sterile 14 Fr catheter and allowed to remain for 5 min. Then the bladder was drained and an additional 50 mL of the ozonated water was instilled and remained until the patient drained her bladder at home, which was on average 3 hours. The bladder instillations were performed 2 times per week.

Table 2: Bladder Instillation Protocol

Timeline of Treatment	Dose
Week 6-9*	100 mL distilled ozonated water twice weekly
Week 10-12	100 mL distilled ozonated water twice weekly
Week 13-18	100 mL distilled ozonated water twice weekly
*: This therapy was initiated on week 6 after the recurrence of ESBL-EC following surgery.	

She was also supplemented with 600 mg of Glutathione and 1000 mg of ascorbic acid via IV following each MAHT infusion. She was placed on a low carbohydrate diet and a probiotic specific to support vaginal flora. After three weeks of therapy with the MAHT and bladder instillations, she had a repeat urine culture which demonstrated 10,000-50,000 colony-forming units of ESBL-EC. She then completed another cycle with weekly MAHT and biweekly bladder instillations for six weeks, resulting in a negative urine culture. She also had a follow-up urinalysis one month after completion of treatment that was negative for infection. Since that time she has had no recurrent symptoms of urinary urgency, dysuria or fever for almost three months.

Discussion

The emerging resistance by bacteria to traditional antimicrobial therapy as noted in the literature is leading to a variety of “super bugs”. This poses a great threat to the human population and other species on the planet. There is documentation for rapid mutation and transfer of plasmids among bacterial organisms that are producing an increasing number of resistant bacteria. There are few options for therapy being developed and this resistance poses a challenge to physicians’ ability to effectively treat bacterial infections. Ozone therapy is known to have potent bactericidal effects without any known bacteria that can resist the effects of ozone when exposed.⁶

Their lack of enzyme systems, such as superoxide dismutase, catalase and glutathione peroxidase which effectively neutralize the oxidative potential of ozone, make this a powerful tool against this emerging epidemic.⁷

These enzyme systems are also involved in protecting cells from the damaging effects of oxidative stress, especially epithelial tissue which can be injured by chronic infection.⁸ When a small ozone dose is well calibrated against the antioxidant capacity of blood by using MAHT therapy, it can trigger several other mechanisms to reactivate the antioxidant system⁹ making MAHT a beneficial therapy for chronic infection providing protection to the cells via upregulation of the antioxidant system.

As ozone therapy improves metabolism and behaves as a cytokine inducer, it can have beneficial influence on infectious disease. Ozone is regarded as the best disinfectant because bacteria are readily oxidized when free in water.^{10, 11} Topical therapy is most effective when used in combination of MAHT leading to the improved oxygenation of hypoxic tissues.⁹

Ozone inactivates bacteria by disrupting the integrity of bacterial cell enveloped through oxidation of phospholipids and lipoproteins.¹² Evidence has also been found that ozone penetrates the cell membrane, reacts with cytoplasmic substances and then converts the closed circular plasmid DNA to open circular DNA, which would seemingly reduce the efficiency of bacterial proliferation¹³. There is additional information that demonstrates that after being exposed to ozone, bacterial cells had collapsed and shrunken patterns, were deformed, had severe rupture and destruction; unlike in the control group.¹⁴ A study by Schwartz et al., showed a decrease of the amount of *E. Coli* 44 times after vaginal insufflation with ozone-oxygen mixture compared to 8 times when using antiseptic solutions.¹⁵ All of these properties make ozone an excellent antibacterial therapy. There is also an immunomodulatory effect which leads to further application in a variety of disease that affect the immune system. Ozone therapy also has a mild activation of the immune system through the synthesis or release of immune-stimulating or immune-suppressing cytokines^{6,16,17}, which are critical to immune-regulation and therefore make it an excellent choice in chronic infectious disease.

Conclusion

The case of chronic cystitis caused by ESBL-EC has limited therapeutic options. However, with the direct bacteriocidal activity of ozonated water and the immunomodulatory effects of Major Autohemotherapy, we have seen one case free of disease for three months following the cessation of treatment. We plan to follow up and perform additional testing to determine if this therapy will result in permanent elimination of this particular strain of bacteria. Further studies are needed to determine the best treatment protocols. In this case, there was disruption of therapy due to the elective surgery which resulted in recurrence of the infection. It is possible that with less disruption of the therapy, she may have had remission earlier in the course of treatment. Based on these limited findings however, there exists the possibility that other resistant bacterial infections may be responsive to a combination of ozone therapies.

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