

Non Antibiotic Alternatives for the Treatment of Urinary Tract Infections Following Spinal Cord Injury.

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ABSTRACT

OBJECTIVE: The objective of this study was to determine the effectiveness of cranberry, uva ursi and echinacea compared to an antibiotic in treating acute urinary tract infections (UTIs) following spinal cord injury (SCI).

DESIGN: Prospective randomized controlled animal study.

METHODS: Female Sprague Dawley rats underwent T9 transection. A urine analysis with culture and sensitivity (UA C&S) was performed 7 days post SCI. SCI rats with documented UTIs were randomized and given amoxicillin or non antibiotic alternatives (uva ursi, cranberry or echinacea) by gastric gavage for 7 days. A UA C&S was done 3 days post antibiotic/ non antibiotic alternative treatment.

Outcome measures: 1. Resolution of bacteria and 2. resolution of white blood cells (WBCs). Treatment considered successful if there was complete resolution in the elevated WBCs. Barnard's Unconditional Test of Superiority Using Difference of 2 Binomial Proportions was used to analyze the data.

RESULTS: *Bacteria Resolution:* Amoxicillin- 42%, uva ursi - 79% , echinacea- 0% and cranberry -0%. Statistical analysis: Amoxicillin, uva ursi, not different in effectiveness at bacterial resolution ($p=0.1$) and statistically superior to echinacea and cranberry ($p = 0.003$, $p = 0.0001$) . *WBC Resolution:* Amoxicillin - 76%, uva ursi - 67% , echinacea - 67% and cranberry - 19%. Statistical analysis: Amoxicillin, uva ursi, and echinacea not different in effectiveness ($p = 0.23$, $p = 0.83$). Amoxicillin , uva ursi , and echinacea statistically superior to cranberry ($p = 0.01$, $p = 0.003$, $p= 0.04$).

CONCLUSIONS: Amoxicillin, uva ursi and echinacea had similar results in the resolution of WBC's (acute UTIs). Cranberry was not effective in treating acute UTIs. This study justifies further research to evaluate side effects, development of resistance, and reoccurrence rates of UTIs using uva ursi, and echinacea.

Key Words: Spinal cord injury, urinary tract infections, treatment

INTRODUCTION

Urinary tract infections (UTI's) are the most common complication in those with SCI.¹ They are a significant cause of morbidity in the spinal cord injured (SCI) population, with sequelae ranging from loss of income and productivity to permanent renal impairment and death.² According to data collected by the National SCI model systems, 74% of all SCI patients experience urinary tract infections while in the acute rehabilitation phase.³ Since those with neurogenic bladders have frequent infections, they are frequently placed on antibiotics. Surveys of people with physical disabilities have found that up to 57 % of individuals with physical disabilities use alternative health care.⁴ Non antibiotic alternatives to treat urinary tract infections which are frequently tried, asked about or written about include cranberry, echinacea, and uva ursi.^{5,6,7}

There are few studies evaluating the effectiveness of antibiotics or non antibiotic alternatives in those with SCI. These studies are not easy to conduct due to the large number of variables that can potentially impact the frequency and treatment urinary tract infections in those with SCI. For example, even with a single type of management, such as intermittent catheterization, variables include gender, frequency of catheterization, type of catheter technique (sterile or clean technique), fluid intake, types of other medications, and type of bladder function.

For this reason, our established SCI animal model was used in this study to help limit the number of variables.^{8,9,10,11} Rats are also a good animal model because there have been multiple studies in rats evaluating various aspects of UTI's, such as bacterial bladder wall adherence and effectiveness of antibiotics.^{12,13,14,15,16} The purpose of this study was to evaluate and identify potentially useful non antibiotic alternatives for the treatment of UTI's in those with SCI.

METHODS

60-day-old female Sprague Dawley rats (Charles River, Wilmington Massachusetts) were housed for two weeks prior to surgery. Lights were on from 0600 to 1800 hours and animals had free access to Purina Rodent chow and tap water.

Rats were deeply anesthetized with sodium pentobarbital (35 mg./100 gm) body weight). A laminectomy was performed at the level of the ninth vertebrae. The spinal cord was exposed and severed under direct visualization. Following surgery, SCI rats were credeed three times a day to express urine from the bladder. This was continued until the animals came out of spinal shock and were voiding effectively on their own with minimal amounts in their bladder to crede. Prophylactic antibiotics (20,000 units procaine penicillin and 25 mg dihydrostreptomycin) were administered the day of and one day post surgery. Post operatively, animals were singly housed in shoe box cages and had free access to Purina rodent chow and tap water. All procedures and surgeries were approved by the Animal Welfare Subcommittee of the East Orange Department of Veterans Affairs Medical Center.

Two weeks post SCI, a midstream urine sample was obtained using crede. The sample was sent for a urine culture and sensitivity (UA C&S). A urine was considered to be positive for a urinary tract infection if bacteria and increased white blood cells (WBC's) were present. The WBC's were considered to be elevated if there were greater than 10

RESULTS:

Bacteria Resolution: Urine cultures were evaluated in animals taking amoxicillin, uva ursi, echinacea or cranberry. The success of various agents at resolving bacteria in the urine were as follows: amoxicillin- 42%, uva ursi - 79% , echinacea- 0% and cranberry – 0%. Statistical analysis: amoxicillin, uva ursi, not different in effectiveness at bacterial resolution ($p=0.1$) and statistically superior to echinacea and cranberry ($p = 0.003$, $p = 0.0001$). There were no samples that had resolution of bacteria with persistent WBC's.

Figure 1.

WBC Resolution: The success of various agents at resolving WBC's in the urine were as follows. amoxicillin - 76%, uva ursi - 67% , echinacea - 67% and cranberry - 19%.

Statistical analysis: amoxicillin, uva ursi, and echinacea not different in effectiveness ($p = 0.23$, $p = 0.83$). Amoxicillin , uva ursi , and echinacea statistically superior to cranberry ($p = 0.01$, $p = 0.003$, $p= 0.04$, respectively). **Figure2.**

There were three patterns of WBC resolutions. The first was WBC resolution and bacterial resolution. The second was bacterial persistence but resolution of WBC's. This was considered as bacterial colonization. **Figure 3.** The third was WBC persistence and bacterial persistence. This was considered as as a urinary tract infection. **Figure 4.**

DISCUSSION

Many individuals with SCI use non antibiotic alternatives to antibiotics in attempts both to prevent and to treat their urinary tract infections. A national telephone survey of the general population conducted in 1991 found that 34% of Americans used at least one alternative therapy to treat a medical condition.¹⁷ Six years later, use of alternative treatments had increased to 42%.¹⁸ Similar findings have been observed in surveys of people with physical disabilities.^{19,20}

This study evaluated three commonly used non antibiotic alternatives to treat urinary tract infections. The three non antibiotic alternatives were cranberry, echinacea, and uva ursi.^{5,21}

Cranberry contains a chemical compound, arbutin, that has been reported to have both an antibiotic and diuretic effect. It also produces hippuric acid in the urine that acidifies the urine, inhibiting bacterial growth.⁵ Cranberry has been shown to lower bacterial adhesion to the bladder while several other fruits: grapefruit, guava, orange, mango and pineapple did not. In theory, reducing bacterial adherence should reduce the incidence of bladder and kidney infections. Cranberry has undergone scientific studies in elderly individuals and found to decrease the risk of kidney infections.²¹ It was not found to reduce bacteriuria in a small series of 15 children with neurogenic bladders.²² It has not been studied for either prevention or treatment in adults with SCI.

Echinacea (*E. purpurea*, *E. angustifolia*, and *E. pallida*), also known as purple coneflower, is reported to be an “immune booster”. The part of the plant that is most frequently used is the root. The substance felt to play the major role in this function is known as echinacoside. Echinacea has been shown to increase T cells and decrease viral and bacterial infections. It has been found to significantly reduce respiratory infections in able bodied individuals.²³ The autonomic system is felt to be a central modulator of immune function. In those with complete cervical SCI, lymphocyte proliferation has been found to be impaired when compared to able bodied individuals. It has been hypothesized that deregulation of the sympathetic autonomic nervous system may contribute to infections in those with SCI.²⁴

In addition to helping the immune system, echinacea has also been found to have antibacterial properties. This is attributed to its ability to inhibit an enzyme hyaluronidase, which is an enzyme in bacteria used to help gain access to a person’s healthy cells. The recommended dose is 500 –1000 mg of the ground herb (1-2 tablets), or 15-25 drops of extract every two hours the first day and then two to three times a day.²⁵ A review article found that no safety concerns were noted other than aversion to taste with the oral use of Echinacea for up to 2 months of continuous use.²⁶ While it is recommended as a way to prevent and treat bladder infections, there have been no studies evaluating its effectiveness.

Uva ursi (*Arctostaphylos uva ursi*) is also referred to as "bearberry" in honor of the bears so fond of its bright red or pink berries. It is frequently recommended as a treatment for urinary tract infections.^{5,6,7} *Uva ursi* is an evergreen shrub. The leaves rather than the berries are used for treatment of bladder infections. The chief constituent of *uva ursi* (bearberry) leaves is a crystallizable glucoside named arbutin. Other constituents are methyl-arbutin, ericolin (an ill-defined glucoside), ursone (a crystalline substance of resinous character), gallic acid, ellagic acid, a yellow coloring principle resembling quercetin, and probably also myricetin. Tannin is present to the extent of 6 to 7%²⁷.

Uva ursi is reported to have antimicrobial, diuretic and astringent properties. Its antimicrobial properties are felt to be due to arbutin, which the body converts into a substance with called hydroquinone.

Uva ursi has been found to be most effective in alkaline urine. Therefore, avoiding substances that acidify the urine such as citrus fruits, tomatoes, and vitamin C supplements is recommended when taking *uva ursi*.²⁷

Official physician handbooks in the United States listed *uva ursi* as a urinary antiseptic for a century up until the 1920s. *Uva ursi* is a popular supplement in Europe. It has been reported to be quite safe when not used for more than 7 days at the suggested doses. The major side effects that may occur in some individuals include nausea and vomiting. However, high doses can cause a disconcerting although apparently harmless greenish-brown discoloration of the urine. Extremely high doses of *uva ursi*, in the range of 10 times greater than the commonly recommended amount, can cause vomiting, ringing in

per high field. Animals with a urine sample consistent with a urinary tract infection were randomized into one of 4 groups: amoxicillin, cranberry, echinacea, or uva ursi. Dosage of each antibiotic and non antibiotic alternative used for treatment was extrapolated, based on rats weighing 250 grams and suggested doses for humans (weighing 70 kg). Suggested human dosages were as follows: cranberry 500 mg three times a day, echinacea 500 mg twice a day, and uva ursi 2-3 ml tincture three times a day.⁵

After 7 days of the non antibiotic alternative and a 3 day washout, a urine analysis and repeat urine sample was obtained. Since WBC's signify tissue invasion, a UTI was considered to be resolved if the repeat urine sample showed the absence of WBC's, even if bacteria were still present.¹

Data was analyzed using Barnard's unconditional test of superiority.

The two outcome measures were the proportion of rats showing the resolution of bacteriuria and the proportion of rats demonstrating a resolution of WBC's.

the ears, shortness of breath, convulsions, and collapse in some cases. Liver damage is also a risk with high doses taken over extended periods of time. It is recommended that those with kidney disease, pregnant women, and breast-feeding mothers should not take uva ursi. because of a lack of information regarding safety.^{27,28}

Uva ursi's effectiveness in those with neurogenic bladders has not been studied. The recommended dose of uva ursi tincture is 2-4 ml three times a day.⁵

This study helps to justify further studies to determine if uva ursi and echinacea are effective in treating UTI's in humans with SCI. There are, however, a number of questions that need to be answered before these antibiotic alternatives can be considered as suitable alternatives to antibiotics. Some of these questions include: what is the optimum dose of uva ursi and echinacea? Is uva ursi and echinacea effective in treating all types of bacteria? These questions are more difficult to answer when evaluating non antibiotic alternatives since these are not purified products. There are also seasonal differences in the concentrations of these substances in their leaves.²⁷ Therefore, it will be very important to standardize the dosages as much as possible. Short and long term side effects of uva ursi and echinacea may be easier to answer since these are popular supplements with widespread use.

It was interesting to note that cranberry supplement were not helpful at treating urinary tract infection despite some studies that have shown cranberry supplements are effective in able bodied individuals.²¹ It is possible that this is because UTI's in those

with SCI frequently have multiple organisms and not the typical E. coli bacteria found in able bodies individuals with uncomplicated UTI's.

CONCLUSIONS: Amoxicillin, uva ursi and echinacea had similar results in the resolution of WBC's (acute UTIs). Cranberry was not effective in treating acute UTIs. This study justifies further studies to evaluate side effects, development of resistance, and reoccurrence rates of UTI's using uva ursi and echinacea .

PERCENT BACTERIA RESOLVED

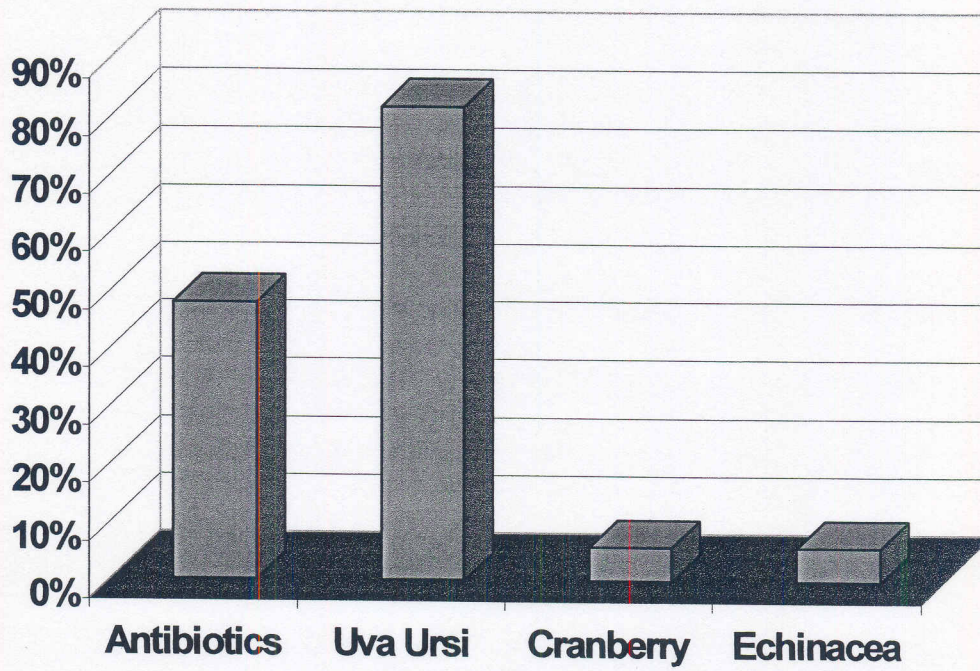


Figure 1.

Percent - WBC (UTI) Resolved

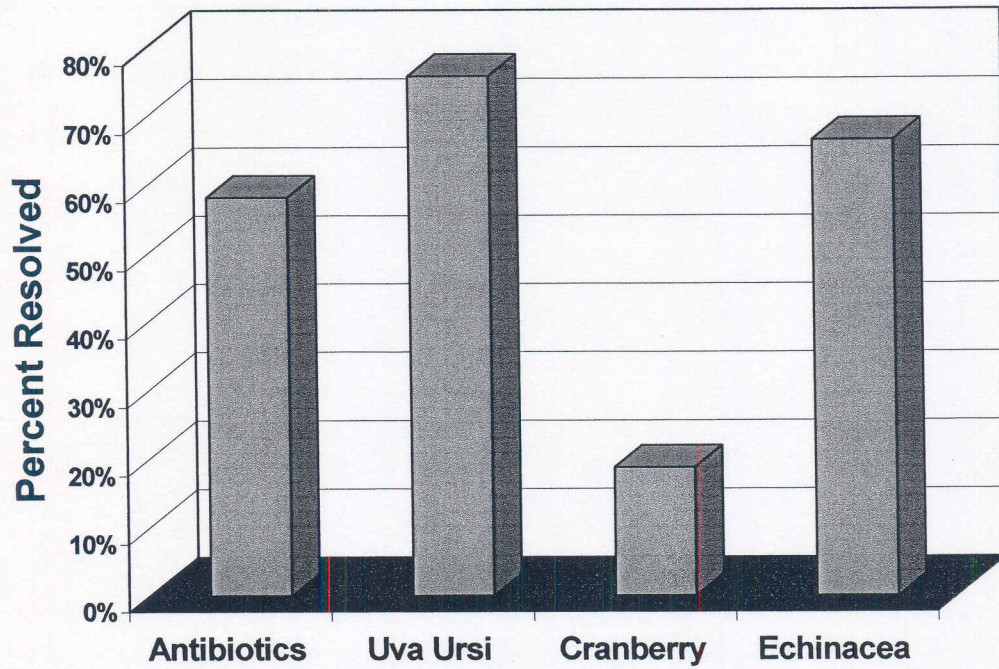


Figure 2.

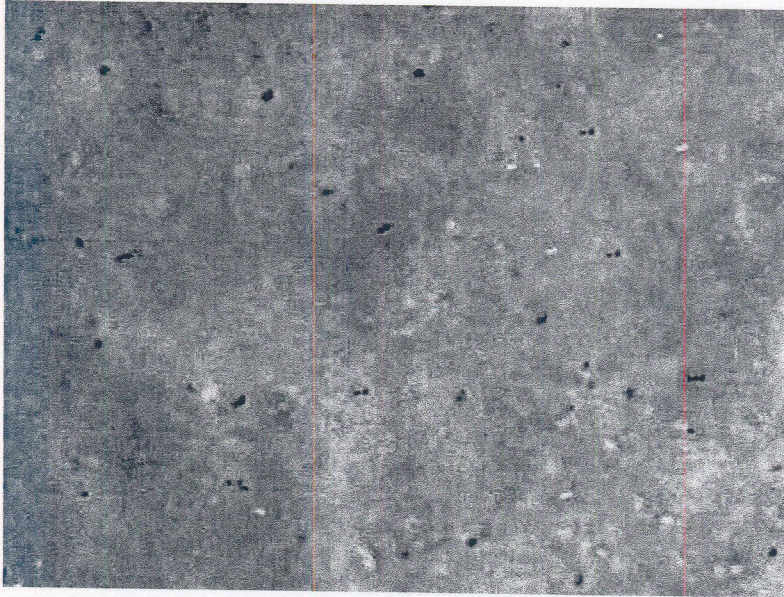


Figure 3. Example of persistent bacteria but no WBC's.

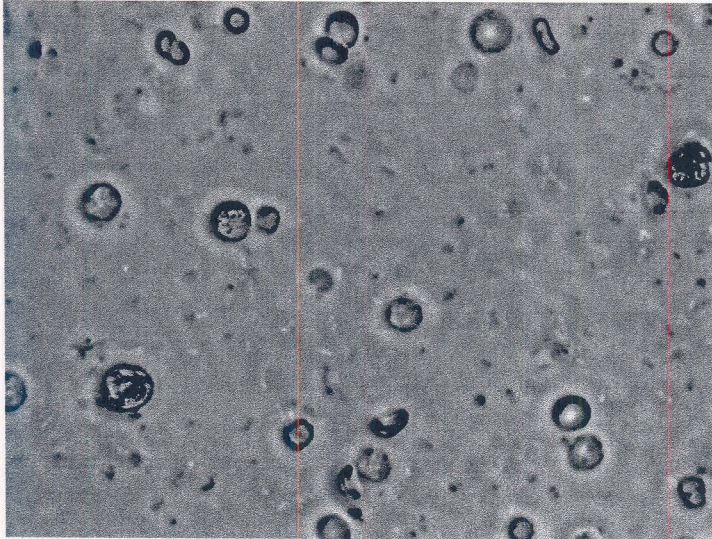


Figure 4. Example of persistent bacteria and WBC's.

Legends

Figure 1. Effectiveness of various tested agents at causing resolution of bacteria in the urine.

Figure 2. Effectiveness of various tested agents at causing resolution of WBC's in the urine.

Figure 3. Example of persistent bacteria but no WBC's.

Figure 4. Example of persistent bacteria and WBC's.

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