



Urinary Tract Infection – A Review on Its Prevalence and Recent Advances

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ABSTRACT

The Urinary Tract Infection (UTI) is a seasonal infection prevalent in coastal areas whose intensity varies among various age groups. *Escherichia coli* is one of the major causative organisms. The current study is to the frequency of UTI in the Coastal region; understand the recent advances in alternative treatment & their efficacy. The known medication for the UTI is quinolones and cephalosporin. Cranberry extract is the only medicine used from a plant source that is expensive and not native to India. The main cause of UTI to spread is a lack of hygiene, sexual intercourse, and inadequate consumption of water. Change in the pH of the urethra during puberty & menopause in women facilitates the growth of opportunistic Uropathogens. Innate immunity can also contribute to the resistance of the body but a recent study says that infection rate varies

among individuals considering their age, immunity, and lifestyle. The pathogens causing UTI are developing resistance against multiple drugs. From this study, we understand that Cranberry is the only plant source for the treatment of UTI in combination with antibiotics. There is a need to understand the importance of improving innate immunity and to know the best treatment regime to treat UTI.

Keywords: Uropathogen; anti-adhesive; nanomedicine; traditional medicine.

ABBREVIATIONS

CNF1 -Cytotoxic factor type 1
 UT - Urinary tract
 UTI -Urinary tract infection
 Upec - Uropathogen *E. coli*
 Mlc -Minimum Inhibitory concentration
 AgNP -SILVER NANOPARTICLES
 CBP - Chronic bacterial prostatitis
 SUC -Standard Urine Culture
 CFU -Colony forming units

1. INTRODUCTION

Urinary tract infection (UTI) is a common disease among young and mature adults but is more prevalent among females. Since females have a short and wider urethra, hence, the chances of colonization of microbes are greater. The cause of the disease is mainly due to catheterization, anatomical abnormalities, and behavioral factors. Children and young adults between 11 and 23 years of age are more susceptible to UTIs [1]. The severity of the infection can be categorized as either acute (limited to the bladder) or chronic (pyelonephritis) and also as uncomplicated; when it occurs in healthy, non-pregnant women with normal urinary tract (UT) structure and function, and complicated; when it occurs in pregnant, diabetic individuals with abnormal urinary tract structure. Symptoms of UTI are dysuria, urinary urgency, frequent urination, fever, and myalgia if the infection is not treated properly it leads to pyelonephritis. If the microbes get transmitted to the gastrointestinal tract or the kidney there can be further complications [2].

The most common pathogens causing UTI are *Escherichia coli*, *Klebsiella pneumoniae*, *Enterococcus species.*, *Streptococcus agalactiae*, *Proteus mirabilis*, *Staphylococcus saprophyticus*, *Viridans streptococci*, *Klebsiella oxytoca*, *Pseudomonas aeruginosa* to list a few. Among these microbes, *E. coli* contributes to about 86% of the infection of UT. UTI can occur in all seasons. However, a spike in the infection can be observed during warm summer [1,2]. Uropathogenic *E. coli* (UPEC) produce exotoxins

such as hemolysin, cytotoxic factor type 1 (CNF1), and colonization factors that have made it a major pathogen causing UTI [3].

This study aims to provide an overview of recent advances in treatment strategies that can be followed to overcome UTI and to better understand the incidence, prevalence, mode of treatment, and efficacy of the disease. A thorough review of the articles was conducted to understand the disease incidence and etiology scenario, along with the latest advancement in the treatment mode and emerging medicine systems [4].

2. DISEASE INCIDENCE

The chances of UTI relapse are very common. Approximately 25% of women have a recurrent infection either by the same pathogen or by another pathogen. Post-menopausal women are more susceptible to re-infection than premenopausal women. Reinfection may be due to behavioral factors or lack of proper treatment. The risk factors for UTI occurrence may include lack of immunity, lack of hygiene, intercourse with multiple partners, and the postmenopausal phase. Recent studies have shown that toll-like receptors, chemokines, and cytokines play a role in disease prevention. However, good personal hygiene and lifestyle are important for UTI prevention [5].

In India, the incidence of UTI is prevalent in all parts of the country, regardless of weather conditions or seasons. Sharma, Netam [6] studied the prevalence of UTI among tribal women in Madhya Pradesh in which *E. coli*, *P. aeruginosa*, and *K. pneumoniae* were the most common pathogens. These pathogens were susceptible to kanamycin, gentamycin, and streptomycin antibiotics. In another study by Valluri Soma Sekhar [7], the prevalence of UTI among patients suffering from diabetes in South India revealed that 35% of the patients were infected by *E. coli*. Kaur and Kaur [8] studied the etiology of UTI among infants in North India; found that *E. coli* and *Klebsiella species* were the common uropathogens.

As the study revealed that pregnant women in mid-trimester pregnancy are more susceptible to infection with 26% of infected individuals were among the volunteers involved in the study and newborns of healthy mothers were healthier than newborns of the infected mother where newborns of healthier mothers weighed 0.44KG more than the newborns of infected mothers [9, 10]. Comparing to non-pregnant women pregnant women are more prone to infection and there is a necessity for urine testing during the early days of pregnancy and pregnant women should be educated on personal sanitary cleanliness, not to overuse antibiotics, and undergo frequent comprehensive urine analysis [11, 12].

The methods of diagnosis for UTI like Standard Urine Culture (SUC), CFU (Colony forming units)-based testing, and *E. coli* centric view of UTI have limitations and a recent study says that diagnostic methods of UTI should be reconsidered because earlier the idea was that the uropathogens caused UTI by invading the sterile urinary bladder whereas the idea of the sterile urinary bladder has been disproved and the diagnostic methods should also be updated to prevent recurrent infection [13, 14]. Another study on the efficiency of using the dipstick to diagnose UTI says that it is accurate only in children above 2 years than for younger children [15].

The host factors such as, short urethra in females and abnormal function of the prostate in males, usage of a spermicide which reduces the vaginal microflora of lactobacilli, post-menopausal women due to lower level of estrogen, neurogenic bladder which reduces the unidirectional flow of urine, renal stones reduce pathogens to flush have very chances of UTI. Along with the structural abnormalities, genetic abnormalities like a defect in the CXCR1 gene expression have been associated with recurrent UTI. In men, High risk of infection is during infancy and early childhood due to Prostatic hyperplasia. [16]. Adult males with a history of hypospadias are also prone to infection [17].

2.1 Pathophysiology

If the Bacterial count of the urine sample is $\geq 10^4$ colony forming units per ml (c.f.u. /ml) can be considered as an infected urine sample accompanied by microscopic examination of the urine. Based on the number of c.f.u./ml the severity of the infection can be determined. If the

count is less than 10^2 c.f.u./ml that it can be considered as low count and diagnosed as acute infection. Usually, females have a high rate of infection because of the short urethra, and males with abnormal function of prostate with high urine retention are sensitive to infection as retention of urine for a longer duration helps bacteria to colonize.

UTI is diagnosed by using a dipstick that detects leukocyte esterase and nitrate reductase activity. Leukocyte esterase activity shows pyuria that is a characteristic feature of inflammation. The nitrate reductase test depends on the detection of nitrites in the urine formed from the nitrates of uropathogens. The first urine of the day is preferred for testing of UTI as the first urine flushes out contaminants. For males foreskin, is usually pulled back while collecting the sample to avoid misinterpretation of the sample [18, 19, 20].

3. TREATMENTS

Consumption of antibiotics, vaccination is the usual treatment regimen for UTI. Also, cranberry juice is a home remedy to get rid of vaginitis and a burning sensation in the genital area due to UTI. Since uropathogens are multidrug-resistant, it is necessary to find a medicinal source or a medicinal system that can act effectively. Apart from conventional medicinal systems, alternative medical systems such as Homeopathy, Unani, herbal medicine, bacteriophage therapy, and nanomedicine have shown promising roles in the treatment of UTI [21]. Ayurveda has many formulations for the treatment of UTI.

3.1 Convention Treatments

3.1.1 Antibiotics

UTI treatment currently relies heavily on antibiotics. The antibiotics most preferred for the treatment of UTI are mentioned in Table 1. Uropathogenic bacteria isolates from the pregnant woman revealed that the pathogens were sensitive to Gentamycin, Nalidixic acid, Nitrofurantoin, Amikacin, and Co-trimoxazole, and resistant to Amoxicillin, Norfloxacin, and erythromycin [22].

3.1.2 Vaccines

For *E. coli* to cause infection cells must adhere to the urinary tract of the mucosa. *E. coli* vaccine development has been targeted to disrupt the

process of cell adhesion, capsules, toxins, and iron metabolism. Vaccines targeting adhesions invade the epithelial cell membrane inside the bladder and promote irreversible bacterial attachment. The recombinant protein MrpH is an anti-adhesin molecule that interferes with the adhesion of *E. coli* fimbriae to attach the epithelial cell to the urinary tract. *E. coli* capsule vaccines act as a regenerative agent that degrades the pathogens and quickly recognizes the pathogens in host immune cells. As the capsule protects the pathogenic cells from host immunity, the destruction of the capsule has a promising effect on the treatment of the infection. α -hemolysin (HlyA) or cytotoxic necrotizing factor-1(CNF1) are toxoids released by uropathogens that promote apoptosis of the host cells causing a deeper infection. Vaccines targeting toxins protect the bladder by preventing toxins from interacting with host epithelial cells. UPEC requires iron for transporting and storing oxygen, vaccines for iron metabolism focuses on reducing the iron availability in the host [24, 25, 26].

3.2 Nanomedicine

Nanoparticles synthesized from various plant extracts are showing promising effects in treating UTI. Zinc nano-particles from *Berberis aristata* & *Passiflora caerulea*, copper-sulfide nanoparticles from *Serratia nematodiphila* silver nanoparticles from *Anogeissus acuminata* are the major nanoparticle components that can be potential drug candidates against UTI [27]. Al-Enizi, Ahamad [28] have successfully prepared copper nanoparticles (CuNPs) in the hydrogel matrix which is effective against UTI pathogens (*K. pneumoniae*, *E. coli*, *P. aeruginosa*, *S. aureus*, *P. vulgaris*, and *P. mirabilis*).

Using *Cissus vitiginea* copper nanoparticle was synthesized which was an efficient antibacterial agent against *E. coli* and *Enterococcus sp.* causing UTI and also against *Klebsiella Species*. Nanoparticles synthesized in an eco-friendly way can be an antibacterial agent against uropathogens [29].

Silver Nanoparticles synthesized in the ethanolic extract of the plant *Mimosa pudica* have excellent antibacterial effects on uropathogens [30] and also from the seeds of *Nigella sativa* inhibited the growth of UPEC and *S. aureus* [31]. Use of polyurethane (PU) catheter modified with tetracycline hydrochloride (TCH) attached silver

nanoparticles embedded PolyRicinoleic acid-Polystyrene [32] and silver nanoparticles synthesized from coral-associated bacteria have shown antibacterial and antibiofilm activity [33]. Nanoparticles along with amoxicillin and trimethoprim have synergistic effects against a majority of the uropathogens especially against UPEC [34]. A synthesized nanoparticle from a hydrogel prepared out of carboxymethyl cellulose (CMC), polyvinyl alcohol (PVA), and the cross-linker ethylene glycol diglycidyl ether (EGDE), followed by the incorporation of AgNPs by microwave radiation exhibited good antibacterial activity against UPEC and *K. pneumoniae* [35].

3.3 Fruits

3.3.1 Cranberry fruit extract as an anti-adhesive agent

The efficacy of fruit extract of cranberry against Tamm-Horsfall Protein in human urine and its anti-adhesive activity against UPEC was investigated. Results indicated inhibition of adhesion of UPEC strain UTI89 to human T24 bladder cells [36]. The glycoprotein THP is characterized by conserved high-mannose moieties, this binds to type 1 fimbriated UPEC. The type 1 fimbriae interact with mannose residues from uroplakin on the surface of uroepithelial cells, which serves as an adhesion receptor for the bacterium as type 1 fimbriae are known to interact with mannose residues from uroplakin on the surface of urothelial cells, THP interferes in the binding of the bacteria to uroplakins.

The chemical constituent of food-grade cranberry dry extract contains flavonoid glycosides, anthocyanidins, A-and B-type proanthocyanidins, phenylpropanoid acid derivatives, benzoic acid derivatives, chlorogenic acid derivatives, and coumaroyl-tryptophan derivatives have anti-adhesive properties. Over a hundred anthocyanidins, bioflavonoids, carbohydrates, chalcones, flavonoids, flavonolignans, glucosinolate, lignans, organic acids, organic alcohols, urolithins have anti-adhesive properties. Anti-adhesion molecules affect the adhesion of UPEC UTI89 to T24 bladder cells under *in-vitro* conditions. Independent experiments have shown that non-glycosylated flavones and flavonols have greater anti-adhesion activity than glycosides exhibited [37,38,39].

Table 1. Antibiotics and their dosage prescribed against uncomplicated UTI [23]

Drug	Dosage
Nitrofurantoin monohydrate/ macrocrystals	100mg twice daily for 5 days
Trimethoprim-sulfamethoxazole	160/800 mg (1 DS tablet) twice daily for 3 days
Fosfomycin trometamol	3-g single-dose sachet
Ciprofloxacin	500 mg twice daily for 5–7 days
Ciprofloxacin XR	1000 mg once daily for 5–7 days
Levofloxacin	750 mg once daily for 5–7 days

The oligosaccharide of cranberry also has anti-adhesive properties. The urine fractions collected from the patients who consumed cranberry juice were tested for anti-adhesion activity by anti-hemagglutination assay with uropathogenic p-fimbriated *E. coli*. As the proanthocyanidins are absorbed by the intestine, the contribution of oligosaccharides was considerable in the anti-adhesive activity of cranberry. The oligosaccharide was found to be arabinoxyloglucan oligosaccharides [40]. In a clinical study of 55 volunteers suffering from UTI, patients were asked to consume cranberry and elderberry extracts. All the patients showed a positive response to cranberry and elderberry extracts [41].

3.3.2 Other fruits and berries

The fruits/herbs having Anti-adhesive properties are *Arctostaphylos uva-ursi* (uvaursi) [42], *Juniperus species* (Juniper), *Mahonia aquifolium* (Oregon grape-Berberidaceae), and *Hydrastis canadensis* (Goldenseal-Ranunculaceae), which are rich in berberine that has anti-adhesive effects on uropathogens. The aqueous extract of corn (*Zea mays*) also reduced the symptoms of UTI significantly [43]. Anti-biofilm activity of *Terminalia arjuna* and *Ipomea carnea* plant extract was studied against the most common UPEC, *P. aeruginosa*, and *S. equorum*. Ethanolic extract of *Ananus cosmos* exhibited antibacterial activity against clinically isolated *Enterococcus* and *Staphylococcus* from the patients having UTI [44].

3.4 Alternative Systems of Medicine

3.4.1 Ayurveda

Ayurveda is one of the major alternative systems of medicine in India, Ayurvedic drugs are being used for treating many urinary tract ailments [45, 46]. A review of ayurvedic drugs against UTI Bhokardankar [47] has listed 37 potent plants. UTI is termed as Mutrakrucha in Ayurveda. Trinetrakhya Ras, Varunadilauh, Mutrakruhantak Ras, Trunpanchmula, Gokshurkath, Haritakyadiyog,

Duralabhadikashaya, Eladi Churna, Tarkeshwar Ras, Varundya Lauh and Chandrakala Ras are the ayurvedic formulation which was used for treating UTI [36]. The listed plants and formulations showed their activity against uropathogens along with antipyretic and diuretic properties. The mode of action was similar to the anti-bacterial and anti-adhesive properties of active ingredients in the formulations.

3.4.2 Homeopathy

The homeopathic system of medicine has its origin in Germany is being considered as one of the most effective systems with lesser side effects. Children and pregnant women prefer this system as there are fewer side effects. Nwabudike has prescribed homeopathic preparations of Phosphorus, Platinum metallicum, Collibacillinum, and Causticum were very effective in treating three women with recurrent UTI. *Thuja occidentalis*, *Lycopodium clavatum*, *Sepia ocinalis*, *Pulsatilla pratensis*, *sulfur*, *Nux vomica*, *Hepar Sulphur*, *Rhus toxicodendron*, *Arnica Montana*, *Calcarea carbonica*, *Tuberculinum bovinum* (Kent), *Natrium muriaticum*, *Carbo vegetabilis*, *Cantharis vesicatoria*, *Staphisagria*, and *Berberis vulgaris* integrated with antibiotics can show significant effect against uropathogens. Rather than acting directly on the pathogens, homeopathic medicine concentrated on boosting innate immunity to eliminate pathogens from the urinary tract [42, 48].

3.4.3 Unani

The cystitis is termed as Warm-e-Masana, pyelonephritis is termed as Warm-e-Kulliya, and UTI is termed as Warm-e-Majra-e-Baul in this system of medicine. Mucilage of *Althaea ocinalis*, *Sphaeranthus indicus*, *Euphorbia hypericifolia*, *Tribulus terrestris*, and *Sharbat Anarshireen* (*Punica granatum*), *Citrullus vulgaris*, and *Cucumis melo* seeds were used as agents to treat UTI. Unani medicines given to the patients suffering from UTI are Sat Behroza, RasSafaid, ShoraQalmi, and Kaphoor. These drugs are administered for one month and two more drugs

i.e Safuf Mudir and Sharbat Bazurimotadil are administered for 21 days. This showed significant improvement in UTI [27].

3.4.4 Essential oils

Essential oils extracted from plants play a significant role as pharmacological agents (Patil, Patil). An anti-microbial study of aqueous and ethanolic extracts of three plants namely *Matricaria chamomilla*, *Silybum marianum*, and *Melissa officinalis* shows a significant effect on uropathogens, especially on UPEC. The anti-microbial property of *Azadirachta indica* is tested against the uropathogens producing β -lactamase enzymes [49, 50]. The essential oil extracted from *T. zygis*, *O. majorana*, and *R. officinalis* exhibited the greatest anti-microbial activity against *E. coli* and enhanced biofilm inhibitory action. The active ingredients cavacrol and thymol essential oils were identified in these plants. A study on anti-microbial activity of essential oils of *Pelargonium graveolens* in combination with ciproflaxin inhibited uropathogens *Klebsiella pneumonia* (KT2), *Proteus mirabilis* (PRT3), and *Staphylococcus aureus* (ST2) [51]. The essential oils from the plants *Ocimum gratissimum*, *Cytopogon citratus*, and *Salvia officinalis* were extracted and subjected to an anti-microbial study against bacterial strains obtained from 100 urine samples.

3.4.5 Herbal medicine

In the current scenario, medicinal plants have been depicted as a boon to treat uncommon health maladies [52, 53]. The synergistic action of Fresh garlic extract along with ciprofloxacin was studied for its anti-microbial property of chronic bacterial prostatitis (CBP) Etiology CBP is UTI relapse, pathogenic bacteria resistance, and inflammatory signs in prostate secretions. The active component of garlic Ajoene and ciprofloxacin combination exert in-vitro anti-virulence properties of *P. aeruginosa* by decreasing virulence factors and biofilm [51].

Tong, Jia [54] isolated *E. coli* from a 72 years old woman suffering from pyelonephritis and evaluated the anti-microbial property of Chinese herbal mixture against the isolated pathogen. The herbal mixture showed its best activity whereas after 4 weeks of the treatment the disease relapsed. In another study, the impact of Chinese herbal mixture on women uncomplicated UTIs induced by fluoroquinolone-resistant strains was investigated. The mixture was effective by eliminating 71.4% among 56

pre-menopausal women suffering from UTI. The mixture was administered to the patients for 10 days. Among 20 patients who showed bacterial inadequacies after the first week follow up 2 of them showed superinfection. Totally 80% of the patients responded well and 14% of the patients showed adverse side effects of nausea and diarrhea.

Bag, Bhattacharyya [55] modern investigation of Cranberry (*Vaccinium macrocarpon*), Horseradish (*Cochlearia armoracia*), Juniper berry (*Juniperus communis*), Goldenseal (*Hydrastis canadensis*), Plantain (*Plantago lanceolata*), Oregon grape (*Berberis aquifolium*), Barberry (*Berberis vulgaris*), Chamomile flower (*Matricaria recutita*), Couch grass (*Agropyron repens*), Cleavers (*Galium aparine*), Nettle (*Urtica dioica*), Echinacea (*Echinacea species.*), Garlic (*Allium sativum*), Cornsilk (Zea mays), and Cinnamon (*Cinnamomum verum*) has shown remarkable effects in treating UTI. The study also reveals that Asparagus (*Asparagus officinalis*), birch (*Betula species.*), couch grass (*Agropyron repens*), goldenrod (*Solidago virgaurea*), horsetail (*Equisetum arvense*), Java tea (*Orthosiphon spicatus*), lovage (*Levisticum officinalis*), parsley (*Petroselinum crispum*) and nettle (*Urtica dioica*) have been approved as part of therapy for the people suffering from UTI as the herbs increase urine volume thus flushing out of the uropathogens.

Tribulus terrestris, *Trachyspermum copticum*, *Cinnamomum verum*, *Hybanthus enneasermus*, *Phyllanthus amarus*, *Moringa oleifera*, *Terminalia chebula*, *Allium sativum*, and *Ocimum sanctum* were listed by Shaheen, Akram [56] as potential herbal drugs with anti-inflammatory, anti-diuretic and anti-microbial properties. Chinese Herbal medicine formulation also has anti-inflammatory, anti-diuretic, anti-microbial properties and anti-adhesive properties against UTI, and also individual plants like *Coptis chinensis* Franch have a broad spectrum of antibacterial activity against bacteria causing especially against *E. coli* [57]. Rafsanjany, Lechtenberg [58] have short-listed 20 effective herbal drugs by a validated selection process for experimental testing. Among the 20 medicinal plants, *Agropyron repens* L. and the stigmata of *Zea mays*. decreased bacterial adhesion (IC₂₅ 630 μ g/mL, IC₅₀ 1040 μ g/mL) by interacting with bacterial outer membrane proteins. Combination of three Plant extracts of *Betula species*. *Orthosiphon stamineus* and *Urtica species* Shown anti-adhesive effects by interacting with T24 cells.

Table 2. Herbal drug activity against uropathogens

Plant	Activity	Pathogens	MIC	Active Compounds/Extract
<i>Matricaria chamomilla</i>	Anti-microbial activity	UPEC	0.11µg/ml	Catechin, Quercetin, and Silymarin
<i>Azadirachta indica</i>	Anti-microbial activity	β-lactamase producing uropathogens	1.56mg/ml	Ethanollic extract
<i>O. majorana</i> & <i>R. officinalis</i>	Biofilm inhibitory action	UPEC	-	Cavacrol and Thymol
<i>Pelargonium graveolens</i>	Anti-microbial activity	<i>K. pneumonia</i> , <i>Proteus mirabilis</i> and <i>Staphylococcus aureus</i>		Essential oils
<i>Salvia officinalis</i>	Anti-microbial activity	<i>Klebsiella</i> and <i>Enterobacter</i> species		Essential oils
Chinese Herbal Mixture	Anti-microbial property	fluoroquinolone-resistant strains	0.1 g/ml	Drug mixture
Garlic	Anti-microbial activity	<i>P. aeruginosa</i>		Ajoene

4. CONCLUSION

Urinary Tract Infection is the most prevalent microbial infection among all age groups can be prevented by following a hygienic lifestyle that includes drinking enough amount of water and also avoiding unsafe sexual intercourse with multiple partners. As the pathogens are multi-drug resistant there are more cases of recurrent UTI. If the infection is not handled properly, it can be chronic. Various antibiotics are being used against pathogens for ages. But the major drawback of using antibiotics is that the pathogens can become resistant and overcome the activity of the antibiotics. Various vaccines are turning out to be good candidates to treat UTI. Hence many studies concentrate on finding herbal drugs for treating the infection. Various herbal formulations are becoming promising candidates against uropathogens by showing anti-bacterial, anti-biofilm, and anti-adhesive activity. Cranberry is a well know herbal candidate which is considered as most effective among many herbal drugs because of its anti-adhesive effect. Consumption of cranberry increased the number of proanthocyanins or oligosaccharides in the urine that targeted the adhesion of pathogens to uroepithelial cells. Recent studies reveal that the proanthocyanins are being digested by the intestine that indicates oligosaccharides of cranberry could be the major candidates to treat UTI. Along with herbal medicines the homeopathic and Unani formulations are acting as immune boosters by enhancing innate immunity. Ayurveda can also be considered as one of the modes of treatment that also has a similar mode of action as herbal

drugs. Insilco studies are being undertaken to determine the exact mode of action of various promising compounds from herbal extracts. Further studies are required to find the active ingredients from herbal extracts and an effective mode of treatment.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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