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Efficacy and safety of preventing catheter-associated urinary tract infection by inhibiting catheter bacterial biofilm formation: a multicenter randomized controlled trial

Wei He^{2†}, Peifen Ma^{1†}, Lu Li^{2†}, Dongmin Wang^{1†}, Xin Li³, Xingqiao Wen⁴, Yi Zuo⁵, Qin Guo⁵, Yanhong Zhang⁵, Ru Cheng⁶ and Zhiping Wang^{1*}

Abstract

Background Catheter-associated urinary tract infection (CAUTI) remains the most significant challenge among hospital-acquired infections (HAIs), yet still unresolved. The present study aims to evaluate the preventive effectiveness of JUC Spray Dressing (name of U.S. FDA and CE certifications, while the medical device name in China is Long-acting Antimicrobial Material) alone for CAUTI without combining with antibiotics and to evaluate the impact of bacterial biofilm formation on CAUTI results on the inserted catheters of patients.

Methods In this multicenter, randomized, double-blind study, we enrolled adults who suffered from acute urinary retention (AUR) and required catheterization in 6 hospitals in China. Participants were randomly allocated 1:1 according to a random number table to receive JUC Spray Dressing (JUC group) or normal saline (placebo group). The catheters were pretreated with JUC Spray Dressing or normal saline respectively before catheterization. Urine samples and catheter samples were collected after catheterization by trial staff for further investigation.

Results From April 2012 to April 2020, we enrolled 264 patients and randomly assigned them to the JUC group ($n = 132$) and the placebo group ($n = 132$). Clinical symptoms and urine bacterial cultures showed the incidence of CAUTI of the JUC group was significantly lower than the placebo group ($P < 0.01$). In addition, another 30 patients were enrolled to evaluate the biofilm formation on catheters after catheter insertion in the patients' urethra (10 groups, 3 each). The results of scanning electron microscopy (SEM) showed that bacterial biofilm formed on the 5th day in the placebo group, while no bacterial biofilm formed on the 5th day in the JUC group. In addition, no adverse reactions were reported using JUC Spray Dressing.

Conclusion Continued indwelling urinary catheters for 5 days resulted in bacterial biofilm formation, and pretreatment of urethral catheters with JUC Spray Dressing can prevent bacterial biofilm formation by forming

[†]Wei He, Peifen Ma, Lu Li, and Dongmin Wang are co-first authors.

*Correspondence:
Zhiping Wang
eryw_zp@126.com

Full list of author information is available at the end of the article

a physical antimicrobial film, and significantly reduce the incidence of CAUTI. This is the first report of a study on inhibiting bacterial biofilm formation on the catheters in CAUTI patients.

Keywords Urinary tract infection, Catheters, Bacterial biofilm on patient catheters, Physical antimicrobial film, Hospital-acquired infections

Introduction

Acute urinary retention (AUR) is an emergency caused by mechanical or dynamic factors that lead to difficulty in urination in men, usually resulted from prostate hyperplasia or urethral stones [1]. Indwelling catheters can help patients with urinary retention urinate, but may cause urinary tract infections (UTIs) due to catheterization operations and opening of the urethral orifice [2]. Catheter-associated urinary tract infection (CAUTI) has become one of the most common hospital-acquired infection, accounting for approximately 40% of all hospital-acquired infections, second only to respiratory infections in terms of incidence [3, 4]. It has been shown that bacterial biofilm formation on the inserted urethral catheter is a key reason for the high incidence and difficulty in treating CAUTI [5]. There are currently reports of in vitro bacterial biofilm tests on catheters and animal in vivo bacterial biofilm tests on catheters [6–8]. However, to our knowledge, there are currently no reports of in vivo bacterial biofilm formation tests on catheters inserted into the patient's urethra. This trial is different from the reported trial of JUC Spray Dressing (name of U.S. FDA and CE certifications, while the medical device name in China is Long-acting Antimicrobial Material) inhibiting biofilm formation on the catheter in vitro [9], and is the first report of an in vivo bacterial biofilm formation test on the catheters inserted into the patient's urethra. JUC Spray Dressing in this study is a product of an international patented technology of 'physical antimicrobial method' (Patent No. ZL201210271421.9), composed of 2% organosilicone double long chain diquaternary ammonium salt and 98% deionized water. When sprayed on objects and body surfaces, it forms a positively-charged antimicrobial film (antimicrobial nanofilm). The negatively charged pathogenic microorganisms are electrostatically killed, thereby achieving physical antimicrobial purpose [10–14].

This study aimed to evaluate the effectiveness of JUC alone in preventing CAUTI without the combination use of antibiotics, and to evaluate the impact of bacterial biofilm formation on CAUTI results on the inserted catheters of patients.

Methods

Patients

This study recruited male patients aged 50–80 years old who required indwelling urethral catheterization for more than 7 days, from April 2012 to April 2020 in

6 hospitals in China. A total of 465 male patients were recruited to determine eligibility. Only 294 patients (aged 50–80 years old) were eligible, and the average age of the placebo group and JUC group was 67.8 and 69.6 years old, respectively. Out of these patients, 264 were assessed for CAUTI. They were randomly assigned to either the JUC group ($n=132$) or the placebo group ($n=132$) (Flowchart of the study see Fig. 1). Additionally, 30 were assessed for catheter biofilm and were also randomly divided into JUC ($n=15$) and placebo ($n=15$) groups. All patients were catheterized due to AUR. Participants were excluded if they had any of the following conditions: (1) body temperature >38.5 °C; (2) white blood cell count >5 per high power field; (3) have used urinary catheters in the last 2 weeks; (4) patients with intermittent self-catheterization; (5) patients with suprapubic / percutaneous nephrostomy; (6) patients who received antibiotic treatment in the last 7–14 days; (7) psychiatric disorders; (8) other immunosuppressive diseases. The patients should be excluded if one of the above exclusion criteria was present. The trial was approved by the Chinese Ethics Committee of Registering Clinical Trials at the WHO International Clinical Trials Registry Platform (approval number: ChiECRCT-2012021), registered at the Chinese Clinical Trial Registry of WHO International Clinical Trials Registry Platform (registration number: ChiCTR-TRC-12002562, 26/06/2012). All procedures were conducted in accordance with the latest version of the Declaration of Helsinki, and all participants signed an informed consent form before participating.

Procedure

Grouping

According to a randomization table, the 294 enrolled patients were randomly assigned in a 1:1 ratio to either the JUC Spray Dressing group (JUC group) or the normal saline (placebo group). Among these patients, 30 underwent a biofilm test.

JUC

JUC Spray Dressing is a spray-type medical liquid dressing registered as a Class III medical device Long-acting Antimicrobial Material in China, produced by NMS Technologies Co., Ltd., and also registered with the U.S. FDA and EU CE. There is also report of an in vitro study on biofilm formation on catheters and a CAUTI clinical study [15].

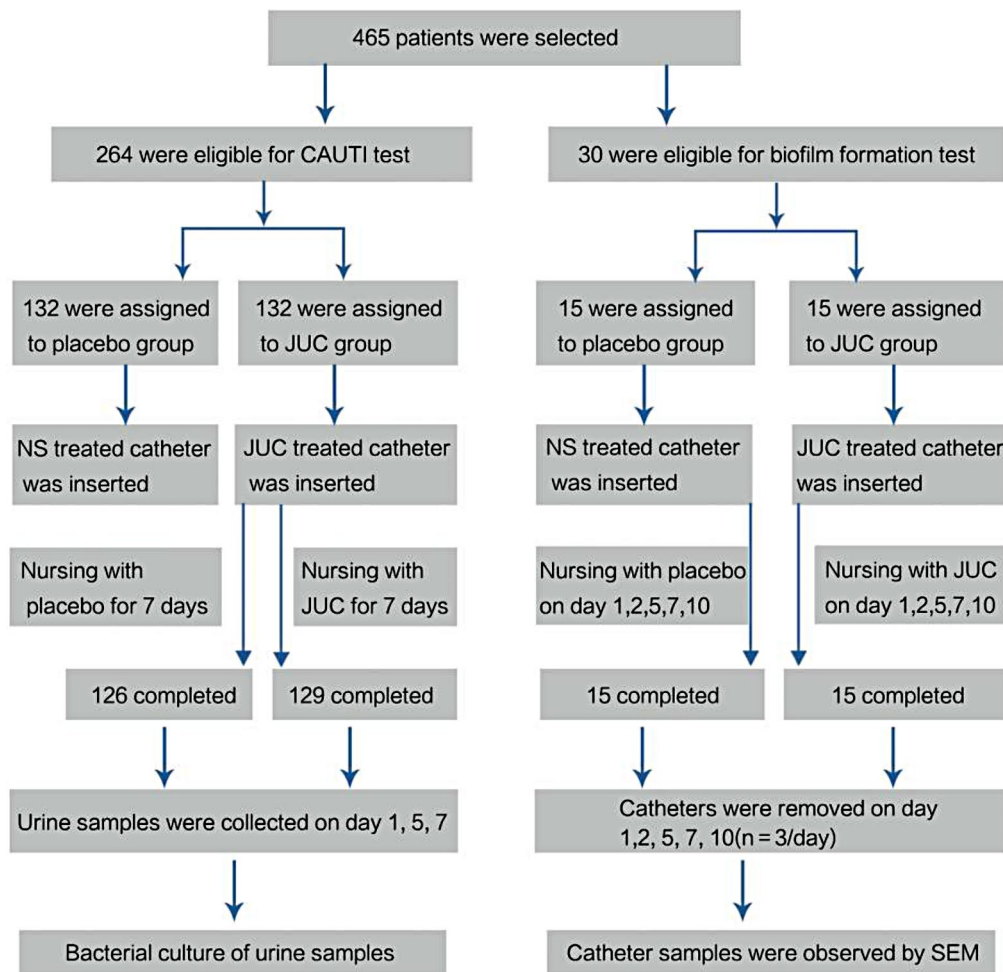


Fig. 1 Flowchart of the study

Blind method

JUC Spray Dressing and placebo (normal saline, NS) were packaged in the same way. All test reagents (JUC and placebo) were consistent in appearance, smell, and skin feel properties. JUC and the same amount of placebo were put into completely identical bottles and sterilized by a high-pressure sterilizer. (From a study safety standpoint, the spray dressing and placebo containers in this study required sterilization. However, it is not necessary when the product enters regular clinical use.) All subjects used catheters with the same brand, and JUC and placebo of the same amount were marked according to a random table. Only the person responsible for packaging knew and recorded the randomization code. Patients and medical staff participating in the trial did not know whether the patient received JUC or placebo. The person responsible for marking could make it unblind only after the study was completed and the Case Report Forms were collected.

Surface treatment of catheters with antimicrobial film

Before catheterization, all external surfaces of all catheters were sprayed with 3 mL JUC or placebo, and the interior surfaces were irrigated with 5mL sterile normal saline or JUC using a sterile syringe. Sterility was maintained during catheterization.

Care

During the post-catheterized care, the perineum, skin and mucous membranes around the urethra were cleaned with saline cotton swabs, and other standard-of-care urinary catheter maintenance measures such as keeping the collection bag below the patient and avoiding dependent catheter tubing loops are regularly recorded, and equally implemented in both study arms. And then JUC or placebo was sprayed on the perineum, catheter surface, and catheter-drainage junction. The distance between the spray nozzle and the skin or catheters was 10–15 cm. All patients were treated with 3–5 sprays each time, twice a day for seven consecutive days.

CAUTI test

UTIs, allergies, and discomfort symptoms were recorded on days 1, 5, and 7 after catheterization, and urine samples were collected aseptically for bacterial culture on days 1, 5, and 7. Bacteria were cultured on MacConkey agar and blood agar. The number of colonies was counted after culturing the urine bacteria. During the trial, if the patient developed an aggravation of infection, allergy, etc., the catheter was removed immediately, systemic antibiotics were given, and the patient was withdrawn from the study.

Biofilm test

To record the formation of bacterial biofilm on the catheter inserted into the patient's urethra. On days 1, 2, 5, 7 or 10 after catheterization, 6 patients' catheters were removed respectively. Each catheter was cut into 3 parts from the bladder segment, urethral segment and extracorporeal segment, and each segment was further divided into 2 parts (one to assess the biofilm on the interior surface of the catheter and the other to assess the biofilm on the exterior surface). A total of 180 pieces were obtained from the 30 catheters and were analyzed

by scanning electron microscopy at 2000x magnification (test method see Fig. 2), to visualize bacterial biofilm formation on catheters over time.

Indicator evaluation

According to the definitions of the Infectious Diseases Society of America and the U.S. Centers for Disease Control and Prevention, CAUTI is defined by the presence of microbiological indicators and symptoms or signs compatible with UTI:

1. Patients with indwelling catheterization for more than 48 h.
2. Presence of at least one bacterial species ≥ 10 colony-forming unit (CFU)/mL in the urine.
3. Presence of at least one of the following symptoms or signs compatible with UTI in the patients:
 - 1) >38 °C; 2) suprapubic tenderness; 3) costospinal angle pain or tenderness; 4) urinary urgency; 5) urinary frequency; 6) chills; 7) dysuria; 8) acute hematuria; 9) pelvic discomfort.

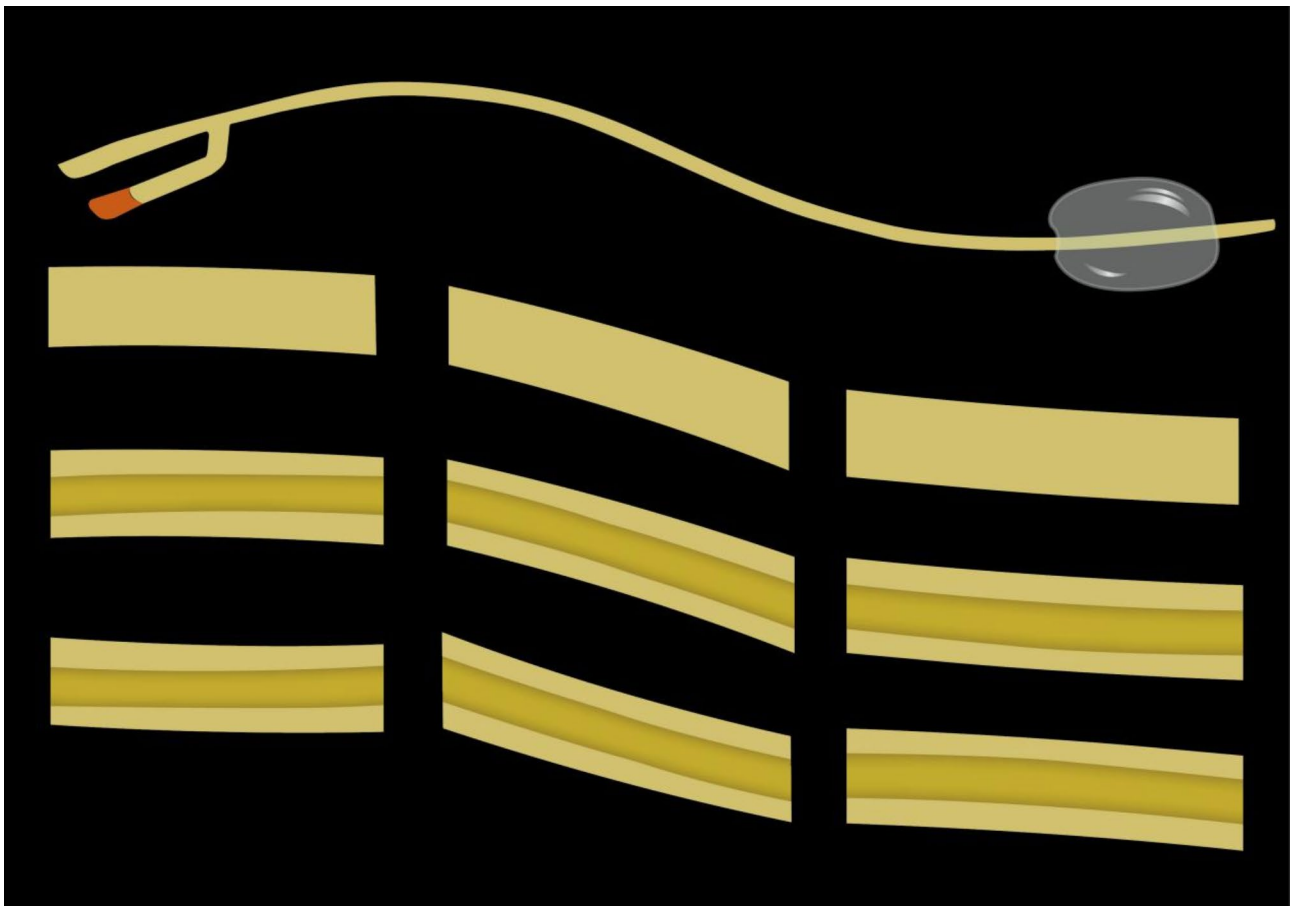


Fig. 2 Biofilm test method

Table 1 Common bacterial typing detected in urine samples

| Bacterial species | Day 5 (number of cases, %) | | Day 7 (number of cases, %) | |
|-----------------------------------|----------------------------|-----------------|----------------------------|-----------------|
| | Control group | Treatment group | Control group | Treatment group |
| <i>Escherichia Coli</i> | 19(15.08%) | 2(1.55%) | 40(31.75%) | 9(6.98%) |
| <i>Enterococcus faecalis</i> | 4(3.17%) | 0 | 1(0.79%) | 1(0.78%) |
| <i>Klebsiella pneumoniae</i> | 2(1.59%) | 1(0.78%) | 3(2.38%) | 2(1.55%) |
| <i>Pseudomonas aeruginosa</i> | 1(0.79%) | 0 | 1(0.79%) | 0 |
| <i>Staphylococcus epidermidis</i> | 3(2.38%) | 0 | 6(4.76%) | 1(0.78%) |
| <i>Staphylococcus aureus</i> | 0 | 0 | 1(0.79%) | 0 |

The primary efficacy indicator is CAUTI (including microbiological indicators and symptoms or signs).

Secondary outcomes were bacterial biofilm formation on the catheters and adverse reactions in patients. After filling out the case report form by visiting, statistical analysis can be performed on the above indicators.

Statistical analysis

All results were analyzed using the SPSS statistical analysis software. Based on the 20% absolute incidence of CAUTI, the number of patients in this study would provide the study with 80% statistical power, a two-sided type I error rate of 5% and a type II error rate of 10%. A non-adherence rate of 10% was also set based on previous investigations. The proportions of patients with primary outcome were compared by conducting a chi-square test and secondary outcome with time-to-event analysis.

Results

Study patients for CAUTI

Complete follow-up data were obtained for 255 participants (126 in the placebo group and 129 in the JUC group) who participated in the CAUTI assessment. Five patients (4 in the placebo group and 1 in the JUC group) were lost to follow-up due to UTI on day 1. Besides, there was one instance of catheter dislodgement (JUC group); Self-removal of the catheter in 3 patients (2 in the placebo group and 1 in the JUC group). $p > 0.05$, there was no statistical difference between the two groups. Among the patients who participated in the biofilm assessment, the catheters were removed on days 1, 2, 5, 7, and 10 after catheterization in both the JUC group and the placebo group (3 patients/group/time, removing the catheter would not affect the treatment, this was to observe the bacterial biofilm, just insert another catheter). $p > 0.05$, there was no statistical difference between the two groups.

Table 2 Comparison of urinary tract infection after catheterization between two groups (number of cases, %)

| Group | Number of cases | Day 1 | Day 5 | Day 7 |
|-----------------|-----------------|-------|--------------|-----------------|
| Treatment group | 129 | 0 | 4 (3.10%) | 15 (11.63%) |
| Control group | 126 | 0 | 30 (23.81%) | 55 (43.65%) |
| P value | | | $p < 0.01^*$ | $p < 0.01^{**}$ |

Notes $*\chi^2 = 23.66, p < 0.01$, in the comparison of urinary tract infection rate between two groups on day 5, there was extremely significant differences

$**\chi^2 = 32.81, p < 0.01$, in the comparison of urinary tract infection rate between two groups on day 7, there was extremely significant differences

Incidence of UTI

Detailed results of bacterial cultures were shown in Table 1. On the 5th day, there were 3 cases of bacteriuria in the JUC group, including 2 cases of *Escherichia coli* and 1 case of *Klebsiella pneumoniae*. The bacteriuria rate was 2.33%. In the placebo group, 29 cases of bacteriuria occurred, including 19 cases of *Escherichia coli*, 4 cases of *Enterococcus faecalis*, 2 cases of *Klebsiella pneumoniae*, 1 case of *Pseudomonas aeruginosa*, and 3 cases of *Staphylococcus epidermidis*. The bacteriuria rate was 23.02%. On the 7th day, urine was collected for bacterial culture before extubation. There were 13 cases of bacteriuria in the JUC group, including 9 cases of *Escherichia coli*, 1 case of *Enterococcus faecalis*, 2 cases of *Klebsiella pneumoniae*, and 1 case of *Klebsiella pneumoniae*. The bacteriuria rate was 10.08%. In the placebo group, there were 52 cases of bacteriuria, including 40 cases of *Escherichia coli*, 1 case of *Enterococcus faecalis*, 3 cases of *Klebsiella pneumoniae*, 1 case of *Pseudomonas aeruginosa*, 6 cases of *Staphylococcus epidermidis*, and 1 case of *Staphylococcus aureus*. The bacteriuria rate was 41.27%. On the 5th day after catheterization, the UTI rate was 4% in the JUC group and 23.81% in the placebo group. The UTI rate was significantly lower in the JUC group compared with the placebo group ($p < 0.01$). On the 7th day, UTI rate (11.63%) was also significantly lower in the JUC group compared with the placebo group (43.65%, $p < 0.01$) (Table 2). Patients with UTI had 9 UTI symptoms within 7 days. In the placebo group, 10 patients (18.2%) had fever, 10 patients (18.2%) had chills, and 9 patients (16.4%) had hematuria. In the JUC group, there were 2 cases of fever (13.3%), 2 cases of chills (13.3%), and 2 cases of hematuria (13.3%).

Study of bacterial biofilm in catheterized patient's urethra

In one of the hospitals where the patients were studied, 30 patients underwent a catheter bacterial biofilm test. The results are listed in Table 3. Figure 3 is the SEM image of the interior of the bladder segment catheter. The placebo group started to form bacterial biofilms from day 5. In the JUC group, no bacterial biofilm was formed, and the formation of an antimicrobial film was seen. Almost no bacterial debris was seen on days 7 and 10 in the JUC group. In addition, as can be seen from Table 3,

Table 3 Number of bacteria on the catheter

| Time points | Catheter segments | Control group | | Treatment group | |
|-------------|-------------------|------------------|------------------|------------------|------------------|
| | | Interior surface | Exterior surface | Interior surface | Exterior surface |
| Day 1 | Intravesical | - | - | - | - |
| | Urethral | + | + | - | - |
| | Extracorporeal | ++ | - | - | - |
| Day 2 | Intravesical | + | + | - | - |
| | Urethral | ++ | ++ | + | - |
| | Extracorporeal | +++ | + | + | + |
| Day 5 | Intravesical | +++ | + | - | + |
| | Urethral | ++ | ++ | + | + |
| | Extracorporeal | +++ | + | + | + |
| Day 7 | Intravesical | +++ | ++ | + | + |
| | Urethral | +++ | ++ | + | + |
| | Extracorporeal | +++ | - | + | + |
| Day 10 | Intravesical | +++ | +++ | + | - |
| | Urethral | +++ | +++ | - | - |
| | Extracorporeal | +++ | + | - | - |

-: No bacteria (negative); + and ++: colony counting < 10⁵ CFU/ml; +++: colony counting ≥ 10⁵ CFU/ml

in the placebo group, there were more bacteria on the interior surface of the catheter than on the exterior surface. According to previous literature, due to the lack of immune cells on the interior surface of the catheter for the bacteria, or rich nutrition of the urine, for catheterized patients, it's easier to have more bacteria on the interior surface of the catheter than on the exterior surface [16].

Safety assessment

No symptoms of itching, allergies, or irritation associated with JUC group or placebo group occurred during the follow-up period.

Discussion

The inclusion criteria for this study were adults suffering from acute urinary retention (AUR) who require catheterization. Urinary retention is commonly observed in males and is often caused by benign prostatic hyperplasia. In the actual study process, all patients who met the criteria for inclusion were male. We aimed to determine whether JUC Spray Dressing is effective in reducing CAUTI without the need to use antibiotics at the same time. The results of scanning electron microscopy (SEM) demonstrated that bacterial biofilm began to form in the placebo group on the 5th day, but no bacterial biofilms were formed in the JUC group on the 5th day. From a clinical point of view, and taking into account previous reports [17, 18], we believe that our results are valid and feasible, and are in line with patient treatment interests. Bacterial biofilm formation on the catheter is the most important cause of CAUTI [19]. In vitro biofilm models on abiotic surfaces have allowed for investigations

into biofilm formation [20], and in vivo study on animal models have confirmed biofilm formation in living bodies [6]. This study was the first report through catheter in vivo to demonstrate that bacterial biofilm can appear on indwelling catheters in 5 days. At the same time, this study is the first report to validate an effective method that can prevent the formation of bacterial biofilm in vivo. World Health Organization (WHO) pointed out that systemic prophylactic antibiotics, bladder irrigation or saline/antibiotic infusion, and application of sterile drainage bags cannot prevent CAUTI [21]. In Tambyah's study, the patients were catheterized with nitrofurantoin-impregnated silicone catheters, silver polyurethane hydrogel catheters, or control catheters. Between medicated catheters and control catheters, there were no significant differences in the incidence of UTI [10]. In the present study, the antimicrobial nano-film formed on catheters was confirmed by SEM. Even 10 days after the application, the antimicrobial nano-film still existed on the interior surfaces of the catheters, and successfully prevented the formation of bacterial biofilm, significantly reducing the incidence of CAUTI.

Due to the limited scale of the trial and limited available resources, we were unable to verify whether participants who did not receive antibiotic prescriptions reported CAUTI after discharge from the hospital. There is also no data on how to treat patients after the study period. Furthermore, this study is limited to elderly men with acute urinary retention, and the findings may not be applicable to other situations in which urinary catheter use is more common and prolonged. In the future, more multicenter and well-designed research should be conducted to further confirm our results.

Conclusion

This study was the first to report on the formation test of bacterial biofilms on catheters of CAUTI patients in the human urethra in vivo, as well as tests aimed at inhibiting the formation of these biofilms. The test results of bacterial biofilm and of using JUC Spray Dressing alone without the use of antibiotics significantly reduces the incidence of CAUTI shows the consistency between these two results. It explores innovative approaches to address the challenge of treating infections caused by bacterial biofilm resistance in the human body, especially treating chronic inflammatory infections, and providing effective and feasible solutions for clinicians to combat drug resistance.

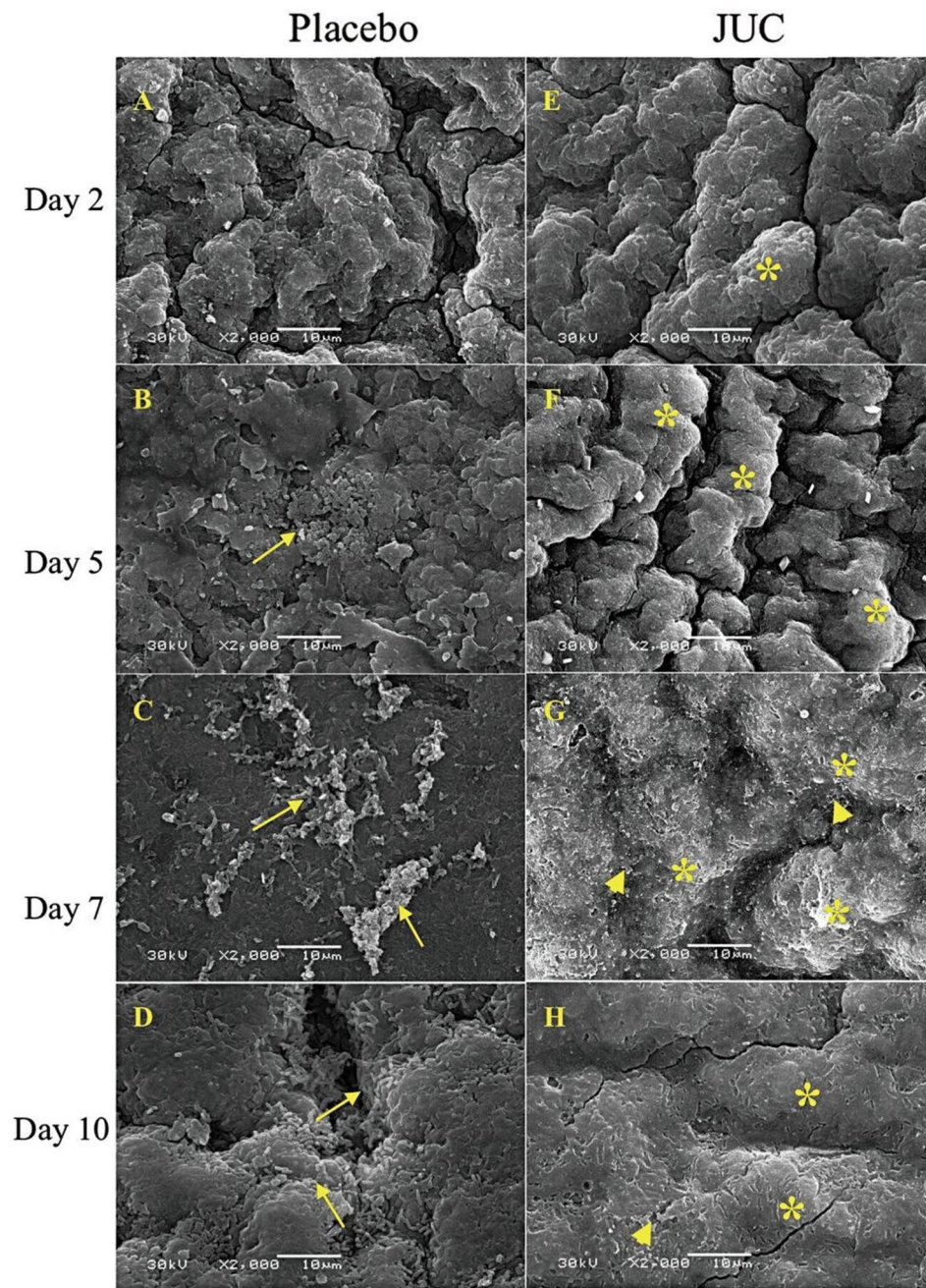


Fig. 3 Scanning electron microscopy (SEM) images of bacterial biofilms and antimicrobial film formed on interior surfaces of the intravesical slices of catheters. **A–D:** In the placebo group, from day 5, a layer of bacterial biofilm formed (indicated by arrowheads) and a large number of bacillus grew in the bacterial biofilm. **E–H:** The antimicrobial film formed in all JUC groups (indicated by asterisks), yet no bacterial biofilm formed, only very few bacterial debris was seen on day 7 and day 10 (indicated by triangles). Scale bars = 10 μm

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Author contributions

HW, MP, LL, WD, LX, and WX designed the study, participated in data collection, analysis, and drafting of the manuscript. WZ, ZY, GQ, ZY, and CR participated in the study design, data analysis, and critically reviewed the manuscript. All authors have read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Registration number and name of trial registry.

The trial was approved by the Chinese Ethics Committee of Registering Clinical Trials at the WHO International Clinical Trials Registry Platform (approval number: ChiECRCT-2012021), registered at the Chinese Clinical Trial Registry of WHO International Clinical Trials Registry Platform (registration number: ChiCTR-TRC-12002562, 26/06/2012).

Competing interests

The authors declare no competing interests.

Author details

¹Lanzhou University Second Hospital, No. 82, Cuiyingmen, Chengguan District, Lanzhou 730030, People's Republic of China

²Tongji Hospital, Tongji Medical College, Huazhong University of Science & Technology, Wuhan, China

³Beijing Hospital, Beijing, China

⁴The Third Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China

⁵Nanfang Hospital, Southern Medical University, Guangzhou, China

⁶Institute of Urology, The Second Hospital of Tianjin Medical University, Tianjin, China

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References

- Bengtson MB, Farkas DK, Borre M, Sørensen HT, Nørgaard M. Acute urinary retention and risk of cancer: population based Danish cohort study. *BMJ*. 2021;375:n2305.
- Chenoweth CE, Urinary Tract I. 2021 Update. *Infect Dis Clin North Am*. 2021;35(4):857–70.
- Mong I, Ramoo V, Ponnampalavanar S, Chong MC, Wan Nawawi WNF. Knowledge, attitude and practice in relation to catheter-associated urinary tract infection (CAUTI) prevention: a cross-sectional study. *J Clin Nurs*. 2022;31(1–2):209–19.
- Clarke K, Hall CL, Wiley Z, Tejedor SC, Kim JS, Reif L, Witt L, Jacob JT. Catheter-Associated urinary tract infections in adults: diagnosis, treatment, and Prevention. *J Hosp Med*. 2020;15(9):552–6.
- Ch'ng JH, Chong KKL, Lam LN, Wong JJ, Kline KA. Biofilm-associated infection by enterococci. *Nat Rev Microbiol*. 2019;17(2):82–94.
- Saini H, Vadekeetil A, Chhibber S, Harjai K. Azithromycin-ciprofloxacin-impregnated urinary catheters avert bacterial colonization, Biofilm formation, and inflammation in a murine model of Foreign-Body-Associated urinary tract infections caused by *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother*. 2017;61(3):e01906–16.
- Ionescu AC, Brambilla E, Sighinolfi MC, Mattina R. A new urinary catheter design reduces in-vitro biofilm formation by influencing hydrodynamics. *J Hosp Infect*. 2021;114:153–62.
- Vargas-Cruz N, Rosenblatt J, Reitzel RA, Chaftari AM, Hachem R, Raad I. Pilot Ex vivo and in Vitro evaluation of a Novel Foley catheter with Antimicrobial Periurethral Irrigation for Prevention of Extraluminal Biofilm Colonization Leading to Catheter-Associated urinary tract infections (CAUTIs). *Biomed Res Int*. 2019;2019:2869039.
- Barford JM, Anson K, Hu Y, Coates AR. A model of catheter-associated urinary tract infection initiated by bacterial contamination of the catheter tip[J]. *BJU Int*. 2008;7(1):67–74.
- Yuen J, Chung T, Loke A. Methicillin-Resistant *Staphylococcus aureus* (MRSA) contamination in bedside surfaces of a hospital ward and the potential effectiveness of enhanced disinfection with an antimicrobial polymer surfactant. *Int J Environ Res Public Health*. 2015;12:3026–41.
- Tam B, Chow S. A preliminary report on the effectiveness of Nanotechnology Anti-microbial Spray Dressing in preventing tenckhoff catheter exit-site infection. *Periton Dialysis Int*. 2014;34:6.
- Wan KA, Ng MY, Wong YT. New horizon on community-acquired methicillin resistant *Staphylococcus aureus* (CA-MRSA) skin and soft tissue infection: nanotechnology antimicrobial spray. *Hong Kong j. Emerg. Med*. 2011;18(6):432–6.
- Li W, Ma X, Peng Y. al. Application of a nano-antimicrobial film to prevent ventilator-associated pneumonia: a pilot study. *Afr J Biotechnol*. 2011;10(10):1926–31.
- Yuen J, Yung J. Medical implications of antimicrobial coating polymers-organosilicon quaternary ammonium chloride. *Mod Chem Appl*. 2013;1:3.
- He W, Ye Z, Wang D. Application of a nanotechnology antimicrobial spray to prevent lower urinary tract infection: a multi urology centers trial[J]. *J TRANSL MED*. 2012;10(Suppl 1):S14.
- Marks LR, Reddinger RM, Hakansson AP. Biofilm formation enhances fomite survival of *Streptococcus pneumoniae* and *Streptococcus pyogenes*. *Infect Immun*. 2014;82:1141–6.
- Yan J, Bassler BL. Surviving as a community: antibiotic tolerance and persistence in bacterial biofilms. *Cell Host Microbe*. 2019;26(1):15–21.
- Razdan K, Garcia-Lara J, Sinha VR, Singh KK. Pharmaceutical strategies for the treatment of bacterial biofilms in chronic wounds. *Drug Discov Today*. 2022;27(8):2137–50.
- Lin Y, Chen J, Zhou X, Li Y. Inhibition of *Streptococcus mutans* biofilm formation by strategies targeting the metabolism of exopolysaccharides. *Crit Rev Microbiol*. 2021;47(5):667–77.
- Lusardi G, Lipp A, Shaw C. Antibiotic prophylaxis for short-term catheter bladder drainage in adults. *Cochrane Database Syst Rev*. 2013;7:CD005428.
- David JS. Bacterial biofilms in patients with indwelling urinary catheters. *Nat Clin Pract Urol*. 2008;11(5):598–608.

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抑制导尿管细菌生物膜形成预防导尿管相关性尿路感染的有效性和安全性： 一项多中心随机对照试验

何玮²⁺，马佩芬¹⁺，李路²⁺，王东敏¹⁺，李欣³，温星桥⁴，左毅⁵，郭琴⁵，张艳红⁵，程茹⁶，及王志平^{1*}

摘要

背景 导尿管相关性尿路感染（CAUTI）仍然是医院获得性感染（HAIs）中最重要的困境，但仍未解决。本研究旨在评估 JUC 喷雾敷料（美国 FDA 和 CE 认证名，中国医疗器械名是长效抗菌材料）单独用于 CAUTI 的预防效果，而不与抗生素联合使用，并评估患者插入导尿管上细菌生物膜形成对 CAUTI 结果的影响。

方法 在中国 6 家医院中，我们招募了患有急性尿潴留（AUR）并需要导尿的成年人进行这项多中心、随机、双盲研究。根据随机数字表，将参与者随机分配为 JUC 喷雾敷料组（JUC 组）或生理盐水（安慰剂组），比例为 1: 1。插管前，分别用 JUC 喷雾敷料或生理盐水预处理导尿管。试验工作人员在导尿管插入后收集尿液样本和导尿管样本以进行进一步调查。

结果 从 2012 年 4 月至 2020 年 12 月，我们招募了 264 名患者，并将其随机分配到 JUC 组（n=132）和安慰剂组（n=132）。临床症状和尿液细菌培养显示，JUC 组的 CAUTI 发生率显著低于安慰剂组（ $P<0.01$ ）。此外，另有 30 名患者被招募评估导尿管插入患者尿道的导尿管上的生物膜形成情况（10 组，每组 3 个）。扫描电子显微镜（SEM）的结果表明，在安慰剂组中，细菌生物膜在第 5 天形成，而在 JUC 组中第 5 天没有细菌生物膜形成。此外，使用 JUC 喷雾敷料未报告任何不良反应。

结论 持续留置尿道导尿管 5 天会导致细菌生物膜形成，而使用 JUC 喷雾敷料预处理尿道导尿管可以通过形成物理抗菌膜防止细菌生物膜形成，并显著降低 CAUTI 发生率。这是第一项关于抑制 CAUTI 患者导尿管上细菌生物膜形成研究的首次报道。

关键词 尿路感染；导尿管；患者导尿管细菌生物膜；物理抗菌膜；医院获

得性感染

*何玮、马佩芬、李路和王东敏为共同第一作者。

*通讯作者:

王志平

eryw_zp@126.com

作者信息的完整列表可在文章末尾找到。

引言

急性尿潴留 (AUR) 是一种紧急情况, 由机械或动态因素引起男性排尿困难, 通常是由前列腺增生或尿道结石引起 [1]。留置导尿管可帮助患有尿潴留的患者排尿, 但可能由于插管操作和尿道口开放而引起尿路感染 [2]。导尿管相关性尿路感染 (CAUTI) 已成为最常见的医院获得性感染之一, 占有所有医院获得性感染的约 40%, 仅次于呼吸道感染 [3-4]。已经表明, 插入尿道导尿管细菌生物膜的形成是 CAUTI 高发和难以治疗的关键原因 [5]。目前有报道体外试验导尿管细菌生物膜试验和动物体内导尿管细菌生物膜试验 [6-8]。然而, 据我们所知, 目前并没有关于导尿管插入患者尿道体内细菌生物膜形成的试验报道。本次试验与已经据报道的 JUC 喷雾敷料 (美国 FDA 和欧

盟 CE 认证名, 中国医疗器械名长效抗菌材料) 在体外阻止导尿管上的生物膜形成的试验不同 [9], 首次报道了导尿管插入患者尿道体内在导尿管上细菌生物膜形成的试验。

本研究中的 JUC 喷雾敷料是一种专利“抗微生物的物理方法”的产品, 由 2% 的有机硅双长链双季铵盐和 98% 去离子水组成。喷在物体和身体表面时, 形成带正电的抗菌膜 (抗菌纳米膜), 带负电的致病微生物产生静电被杀灭, 从而实现物理抗菌目的 [10-14]。

本研究旨在评估 JUC 单独预防 CAUTI 的有效性, 而不联合抗生素使用, 并评估其对插入患者尿道导尿管上细菌生物膜形成对 CAUTI 结果的影响。

方法

患者

本试验招募了 50-80 岁需要尿道导尿

管留置超过 7 天的男性患者，从 2012 年 4 月至 2020 年 4 月在中国 6 家医院进行。共招募了 465 名男性患者进行资格评估。只有 294 名患者 (50-80 岁) 符合资格，安慰剂组和 JUC 组的平均年龄分别为 67.8 岁和 69.6 岁。其中 264 名接受了 CAUTI 评估，患者被随机分为 JUC 组 (n=132) 和安慰剂组 (n=132) (研究流程图见图 1)。另外 30 名接受了导尿管生物膜评估，患者被随机分为 JUC 组 (n= 15) 和安慰剂组 (n= 15)。所有患者均因 AUR 接受导尿管插入。如果出现以下情况，则排除参与者：1) 体温 > 38.5℃；2) 白细胞计数 > 5 个/高倍视野；3) 过去 2 周使用过尿道导尿管；4) 间歇性自我导尿的患者；5) 经皮肾造瘘/经皮肾造瘘的患者；6) 在过去 7-14 天内接受抗生素治疗的患者；7) 精神障碍；8) 其他免疫抑制性疾病。如果存在上述任一排除标准，则应排除患者。该试验获得了世界卫生组织国际临床试验注册平台中国临床试验注册处 (批准号：

ChiECRCT-2012021)，在世界卫生组织国际临床试验注册平台中国临床试验注册处进行了注册 (注册号：ChiCTR-TRC-12002562, 2012 年 6 月 26 日)。所有程序均按照《赫尔辛基宣言》的最新版本进行，所有参与者签署知情同意后书后进行。

程序

分组

根据随机数表，按照 1:1 的比例，将纳入的 294 名患者随机分配为 JUC 喷雾敷料组 (JUC 组) 或生理盐水 (安慰剂组)，其中 30 名生物膜试验。

JUC

JUC 喷雾敷料是中国南京神奇科技开发有限公司生产的中国三类医疗器械注册的长效抗菌材料医用液体喷雾型敷料，同时也在美国 FDA 注册和 CE 认证及欧盟注册。并且有一篇体外导尿管生物膜试验和 CAUTI 临床研究文献报道[15]。

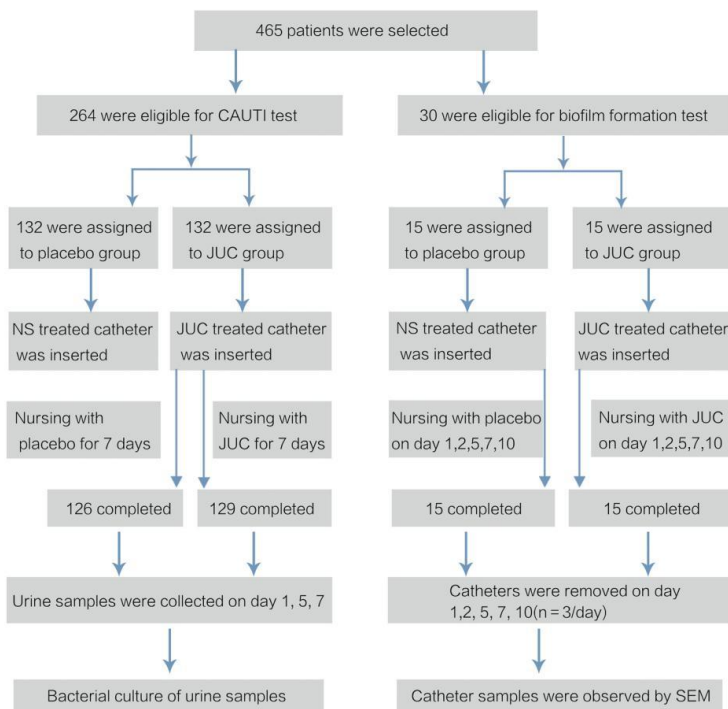


图 1 研究流程图

盲法

JUC 喷雾敷料和安慰剂(生理盐水, NS) 以相同方式包装。所有测试试剂(JUC 和安慰剂) 在外观, 气味和皮肤感觉特性上保持一致。 JUC 和相同数量的安慰剂被放入完全相同的瓶子中, 并通过高压灭菌器进行消毒(从研究安全的角度, 在本研究中喷雾敷料和安慰剂容器需要灭菌。但产品进入常规临床使用时则无必要)。所有受试者使用相同品牌的导尿管, 并根据随机表标记相同数量的 JUC 和安慰剂。只有负责包装的人知道并记录随机化代码。参加试验的患者和医务人员不知

道患者是否接受了 JUC 或安慰剂。直到研究结束并收集了病例报告表之后, 负责标记的人才能使其不透明。

导尿管表面抗菌膜处理

导尿管插入前, 将所有导尿管的所有外部表面喷洒 3 mL JUC 或安慰剂, 并用无菌注射器用 5mL 无菌生理盐水或 JUC 灌洗内部表面。在导尿管插入期间保持无菌状态。

护理

在导尿管插入后护理期间, 用盐水棉签清洁会阴部, 尿道周围皮肤和黏膜, 并定期记录了其他标准护理导尿管维护措施, 如将收集袋放在病人下方, 避免依赖性导尿管管路环, 且这些措

施在两个研究组中都得到了同等的执行。然后在会阴部，导尿管表面和导尿管排放连接处喷洒 JUC 或安慰剂。喷嘴与皮肤或导尿管之间的距离为 10-15 厘米。所有患者每次使用 3-5 次，每天两次，连续七天。

CAUTI 试验

在导尿管插入后 1、5 和 7 天记录尿路感染、过敏和不适症状，并于第 1、5 和 7 天无菌采集尿液样本进行细菌培养。细菌在 MacConkey 琼脂和血液琼脂中培养。在培养尿液细菌后，计算菌落数。在试验期间，如果患者出现感染加重、过敏等情况，立即拔除导尿管，全身给予抗生素治疗，并退出研究。

生物膜试验

记录导尿管插入患者尿道内细菌生物膜形成。30 名患者导尿管置入后在第 1、2、5、7 和 10 天分别取出 6 名患者的导尿管，并将每一个导尿管按膀胱区、尿道区和体外区分别切三段，每

一段再切二片（其中一片检测导尿管的内表面生物膜，另一片检测导尿管外表面的生物膜），30 个导尿管共切 180 片通过扫描电子显微镜在 2000 倍放大率下进行分析（测试方法如图 2 所示），可视化导尿管细菌生物膜的形成及时间。

指标评估

根据美国传染病学会和美国疾病控制中心的定义，CAUTI 是指存在与泌尿道感染相符的微生物学和症状或体征：

1. 留置导尿管超过 48 小时的患者；
2. 尿液中至少有一种细菌种类 ≥ 10 个菌落形成单位 (CFU) /mL。
3. 患者出现以下至少一种症状或体征与 CAUTI 相符：
 - 1) $>38^{\circ}\text{C}$ ；
 - 2) 耻骨上区压痛；
 - 3) 肋脊角疼痛或压痛；
 - 4) 尿急；
 - 5) 尿频；
 - 6) 寒战；
 - 7) 排尿困难；
 - 8) 急性血尿；
 - 9) 盆腔不适。

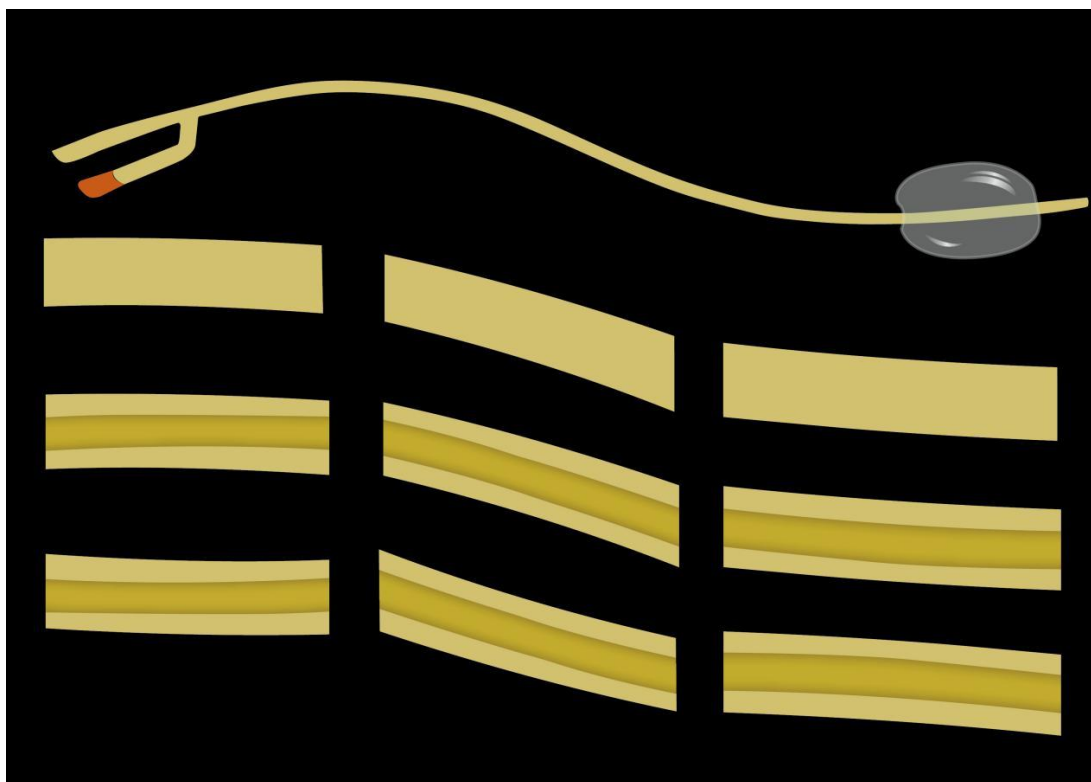


图 2 生物膜试验方法

表 1. 尿样中检测到的常见细菌分型情况

| 常见菌种 | 第 5 天 (例, %) | | 第 7 天 (例, %) | |
|---------|--------------|----------|--------------|----------|
| | 对照组 | 治疗组 | 对照组 | 治疗组 |
| 大肠杆菌 | 19(15.08%) | 2(1.55%) | 40(31.75%) | 9(6.98%) |
| 粪肠球菌 | 4(3.17%) | 0 | 1(0.79%) | 1(0.78%) |
| 克雷伯氏肺炎菌 | 2(1.59%) | 1(0.78%) | 3(2.38%) | 2(1.55%) |
| 绿脓杆菌 | 1(0.79%) | 0 | 1(0.79%) | 0 |
| 表皮葡萄球菌 | 3(2.38%) | 0 | 6(4.76%) | 1(0.78%) |
| 金黄色葡萄球菌 | 0 | 0 | 1(0.79%) | 0 |

主要有效性指标为 CAUTI (包括微生物学和症状或体征)。

次要结果是导尿管上的细菌生物膜形成和患者不良反应。填写案例报告表后, 可以对上述指标进行统计分析。

统计分析

所有结果都采用 SPSS 统计分析软件进行分析, 基于 CAUTI 20%的绝对发生率, 在本研究中的患者数量将为该研究提供 80%的统计功率、双侧 I 型错误为 5%和 II 型错误率为 10%。根据以前的调查结果, 还设置了 10%的不遵从率。通过进行卡方检验比较主要结局的患者比例和时间事件分析比较次要结局。

结果

CAUTI 研究患者

对于参加 CAUTI 评估的 255 名参与者 (安慰剂组 126 名, JUC 组 129 名),

获得了完整的随访数据。由于尿路感染，第 1 天失去了 5 名患者（安慰剂组 4 名，JUC 组 1 名）。此外，有 1 例导尿管滑脱（JUC 组）；3 名患者自行拆除导尿管（安慰剂组 2 名，JUC 组 1 名）。 $p>0.05$ ，两组统计学无差异。在参加生物膜评估的患者中，导尿管在插管后的第 1、2、5、7 和 10 天在 JUC 组和安慰剂组中均拆除（每组 3 名患者/时间，取出导尿管不会影响治疗，这是为了观察细菌生物膜情况，再插一根导尿管即可。）。 $p>0.05$ ，两组统计学无差异。

表 2: 两组插管后尿路感染病例数比较（例，%）

| 组别 | 例数 | 第 1 天 | 第 5 天 | 第 7 天 |
|-----|-----|-------|-------------|---------------|
| 治疗组 | 129 | 0 | 4 (3.10%) | 15 (11.63%) |
| 对照组 | 126 | 0 | 30 (23.81%) | 55 (43.65%) |
| P 值 | | | $p<0.01^*$ | $p<0.01^{**}$ |

注：* $\chi^2=23.66$, $P1<0.01$ ，第 5 天两组症状性 CAUTI 感染率比较，有极显著性差异。

** $\chi^2=32.81$, $P2<0.01$ ，第 7 天两组症状性 CAUTI 感染率比较，有极

显著性差异。

尿路感染发生率

细菌培养的详细结果如表 1 所示。第 5 天，JUC 组出现 3 例菌尿症，其中 2 例为大肠杆菌，1 例为肺炎克雷伯菌。菌尿率为 2.33%。安慰剂组发生菌尿症 29 例，其中大肠杆菌 19 例，粪肠球菌 4 例，肺炎克雷伯菌 2 例，铜绿假单胞菌 1 例，表皮葡萄球菌 3 例。第 7 天，拔管前收集尿液进行细菌培养。JUC 组有 13 例菌尿症，包括 9 例大肠杆菌、1 例粪肠球菌、2 例肺炎克雷伯菌和 1 例表皮葡萄球菌。菌尿率为 10.08%。安慰剂组有 52 例菌尿症，其中大肠杆菌 40 例，粪肠球菌 1 例，肺炎克雷伯菌 3 例，1 例铜绿假单胞菌，6 例表皮葡萄球菌，1 例金黄色葡萄球菌。菌尿率为 41.27%。在导尿后第 5 天，JUC 组的尿路感染率为 4%，安慰剂组为 23.81%。与安慰剂组相比，JUC 组的尿路感染率显著降低 ($p<0.01$)。第 7 天，与安慰剂组 (43.65%， $p<0.01$) 相比，JUC 组的尿路感染率 (11.63%) 也显著降低 (表 2)。尿路感染患者在 7 天内出现 9 种尿路感染症状。安慰剂组中，有 10 名患者 (18.2%) 发烧，10 名患者有寒战，9 名患者 (16.4%) 血尿。在 JUC 组中，有 2 例发烧 (13.3%)，

2 例发冷 (133%) 和 2 例血尿 (13.3%)。

研究导尿管在患者尿道中细菌生物膜

在所研究的患者中的一个研究医院 30 名患者进行导尿管细菌生物膜试验。结果列于表 3 中。图 2 是膀胱段导尿管内部的 SEM 图像。安慰剂组从第 5 天开始形成细菌生物膜。在 JUC 组中, 没有形成细菌生物膜, 并且看到了抗菌膜的形成。在 JUC 组的第 7 天和第 10 天几乎没有看到细菌残留物。此外, 从表 3 可以看出, 在安慰剂组中, 导尿管内表面上的细菌比外表面上的细菌多。根据以前的文献, 由于导尿管内表面缺乏细菌的免疫细胞或尿液的丰富营养, 对于留置导尿管的患者来说, 在导尿管内表面上有更多的细菌比外表面上的细菌更容易[16]。

表 3. 导尿管上的细菌数量

| 时间点 | 导尿管段 | 对照组 | | 治疗组 | |
|-------|------|------|------|------|------|
| | | 内部表面 | 外部表面 | 内部表面 | 外部表面 |
| 第 1 天 | 膀胱 | - | + | - | - |
| | 尿道 | + | + | - | - |
| | 体外 | ++ | - | - | - |
| 第 2 天 | 膀胱 | + | + | - | - |
| | 尿道 | ++ | ++ | + | - |
| | 体外 | +++ | + | + | + |
| 第 5 天 | 膀胱 | +++ | + | - | + |
| | 尿道 | ++ | ++ | + | + |

| | | | | | |
|--------|----|-----|-----|---|---|
| | 体外 | +++ | + | + | + |
| 第 7 天 | 膀胱 | +++ | ++ | + | + |
| | 尿道 | +++ | ++ | + | + |
| | 体外 | +++ | - | + | + |
| 第 10 天 | 膀胱 | +++ | +++ | + | - |
| | 尿道 | +++ | +++ | - | - |
| | 体外 | +++ | + | - | - |

-: 无细菌 (阴性); + and ++: 菌落计数 10^5 CFU/ml; +++: 菌落计数 $\geq 10^5$ CFU/ml

安全评估

在随访期间未出现与 JUC 或安慰剂相关的瘙痒, 过敏或刺激症状。

讨论

本试验的纳入标准为患有急性尿潴留 (AUR) 并需要导尿的成年人, 尿潴留常见于男性, 多由良性前列腺增生引起, 在实际的试验过程中, 最终符合条件纳入试验的患者均为男性。我们旨在确定 JUC 喷雾敷料是否有效降低 CAUTI 而不需要同时使用抗生素。扫描电子显微镜 (SEM) 的结果表明, 在安慰剂组中, 第 5 天开始形成了细菌生物膜, 但在 JUC 组中第 5 天没有形成细菌生物膜。从临床角度来看, 并考虑到以前的报告[17, 18], 我们认为我

们的结果是有效和可行的，并且符合患者治疗利益。导尿管细菌生物膜的形成是 CAUTI 最重要的原因[19]。无机表面上体外生物膜模型已允许对生物膜形成进行调查[20]，动物模型上的体内研究已确认了活体内生物膜形成[6]。本研究首次报道通过人体内导尿管证明了细菌生物膜可以在留置导尿管 5 天出现。同时，这项研究是第一次报道验证了一种有效的方法，可以阻止体内细菌生物膜的形成。世界卫生组织（WHO）指出，全身性预防性抗生素、膀胱冲洗或盐水/抗生素输注以及使用无菌引流袋均无法预防 CAUTI [21]。在 Tambyah 的研究中，患者使用了硝基呋喃酮浸渍的硅胶导尿管、银聚氨酯水凝胶导尿管或对照导尿管进行导尿管置入。在药物涂层导尿管和对照导尿管之间，尿路感染的发生率没有显著差异[10]。在本研究中，扫描电镜证实了导尿管上形成的抗菌纳米膜。即使在应用后 10 天，抗菌纳米膜仍然存在于导尿管内部表面，并成功防止了细菌生物膜的形成，显著降低了 CAUTI 的发生率。

由于试验规模有限且可用资源有限，我们无法验证未接受抗生素处方的参与者在出院后是否报告了 CAUTI。也没有关于如何在研究期后治疗患者的数据。此外，本研究限于急性尿潴留的老年男性这一患者人群，这项研究的发现可能不适用于其他常见和长期使用导尿管的情况。未来应进行更多的多中心和良好设计的研究以进一步确认我们的结果。

结论

首次报道第一篇关于人体尿道体内 CAUTI 患者导尿管上细菌生物膜形成试验，以及抑制细菌生物膜形成试验。细菌生物膜的试验结果与在没有使用抗生素的情况下单独使用 JUC 喷雾敷料可以显著降低 CAUTI 发生率结果显示这两个结果的一致性关系。为人体细菌生物膜耐药性导致的感染，特别是慢性感染炎症治疗难题探索创新的方法，并且并为临床医生提供有效和可行的应对耐药解决方案。

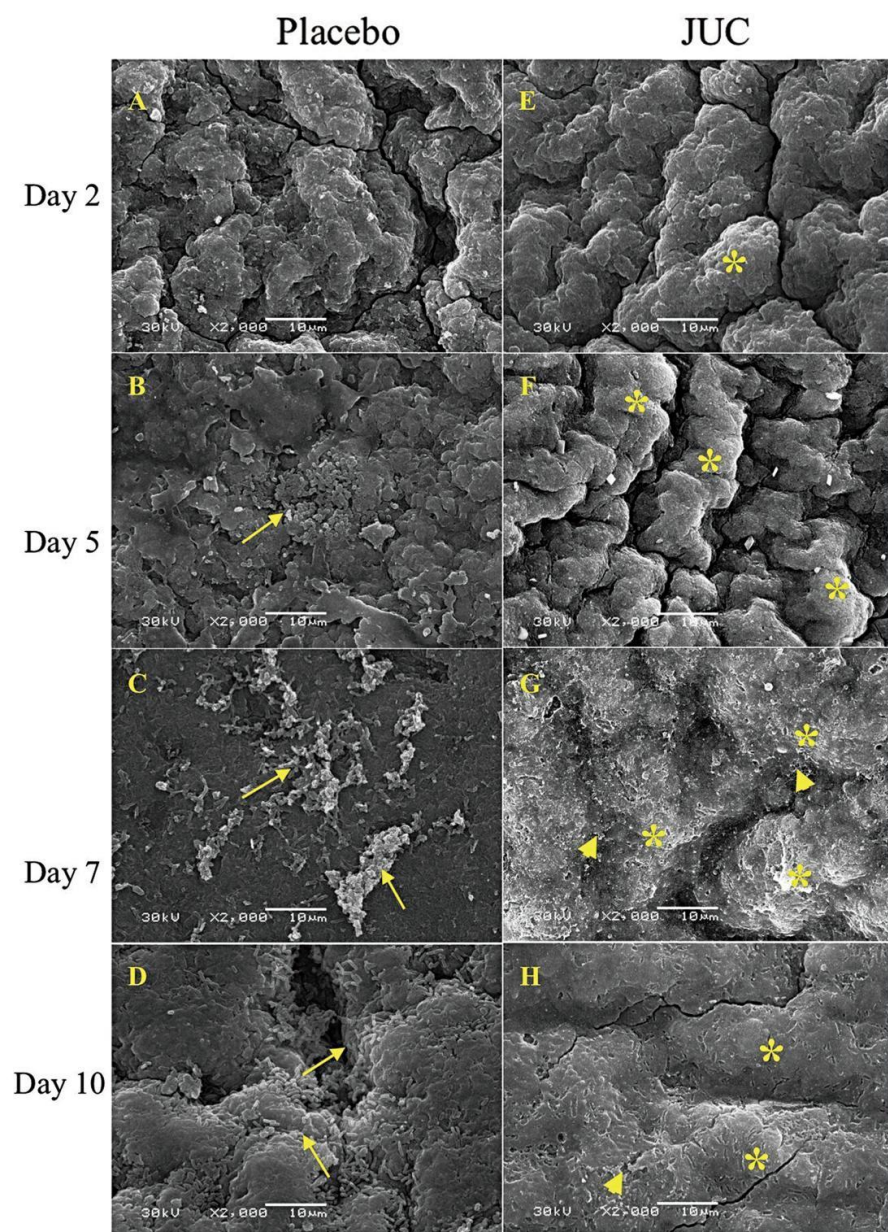


图 3 膀胱导尿管段内部片表面形成的细菌生物膜和抗微生物膜扫描电子显微镜 (SEM) 图像。A-D: 安慰剂组从第 5 天起形成一层细菌生物膜 (箭号标识), 细菌生物膜中生长有大量杆菌。E-H: JUC 组都形成的抗微生物膜 (星号标识), 但无细菌生物膜形成, 只有第 7 天和第 10 天有极少量细菌碎片 (三角形标识)。比例尺=10 μm。

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HW、MP、LL、WD、LX 和 WX 设计了研究，参与了数据收集、分析和手稿的起草。WZ、ZY、GQ、ZY 和 CR 参与了研究设计、数据分析和对手稿的重要审查。所有作者都阅读并批准了最终手稿。

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数据可用性

在当前研究中没有生成或分析数据集。

声明

试验注册号及名称

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竞争利益

所有作者声明他们没有竞争利益。

作者详情

1. 兰州大学第二医院，中国兰州城关区翠英门 82 号，730030
2. 华中科技大学同济医学院附属同济医院，中国武汉
3. 北京医院，中国北京
4. 中山大学附属第三医院，中国广州
5. 南方医科大学南方医院，中国广州
6. 天津医科大学附属第二医院泌尿外科研究所，中国天津

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参考文献

1. Bengtson MB, Farkas DK, Borre M, Sørensen HT, Nørgaard M. Acute urinary retention and risk of cancer: population based Danish cohort study. *BMJ*. 2021;375:n2305.
2. Chenoweth CE. Urinary Tract Infections: 2021 Update. *Infect Dis Clin North Am*. 2021;35(4):857-870.
3. Mong I, Ramoo V, Ponnampalavanar S, Chong MC, Wan Nawawi WNF. Knowledge, attitude and practice in relation to catheter-associated urinary tract infection (CAUTI) prevention: A cross-sectional study. *J Clin Nurs*. 2022;31(1-2):209-219.
4. Clarke K, Hall CL, Wiley Z, Tejedor SC, Kim JS, Reif L, Witt L, Jacob JT. Catheter-Associated Urinary Tract Infections in Adults: Diagnosis, Treatment, and Prevention. *J Hosp Med*. 2020;15(9):552-556.
5. Ch'ng JH, Chong KKL, Lam LN, Wong JJ, Kline KA. Biofilm-associated infection by enterococci. *Nat Rev Microbiol*. 2019;17(2):82-94.
6. Saini H, Vadekeetil A, Chhibber S, Harjai K. Azithromycin-Ciprofloxacin-Impregnated Urinary Catheters Avert Bacterial Colonization, Biofilm Formation, and Inflammation in a Murine Model of Foreign-Body-Associated Urinary Tract Infections Caused by *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother*. 2017 Feb 23;61(3):e01906-16..
7. Ionescu AC, Brambilla E, Sighinolfi MC, Mattina R. A new urinary catheter design reduces in-vitro biofilm formation by influencing hydrodynamics. *J Hosp Infect*. 2021 Aug;114:153-162.
8. Vargas-Cruz N, Rosenblatt J, Reitzel RA, Chaftari AM, Hachem R, Raad I. Pilot Ex Vivo and In Vitro Evaluation of a Novel Foley Catheter with Antimicrobial Periurethral Irrigation for Prevention of Extraluminal Biofilm Colonization Leading to Catheter-Associated Urinary Tract Infections (CAUTIs). *Biomed Res Int*. 2019 Dec 23;2019:2869039.

9. Barford JM, Anson K, Hu Y, Coates AR. A model of catheter-associated urinary tract infection initiated by bacterial contamination of the catheter tip[J]. *BJU Int.* 2008;7;102(1):67-74.
10. Yuen J, Chung T, Loke A. Methicillin-Resistant *Staphylococcus aureus* (MRSA) contamination in bedside surfaces of a hospital ward and the potential effectiveness of enhanced disinfection with an antimicrobial polymer surfactant. *Int. J. Environ. Res. Public Health.* 2015; 12, 3026-3041
11. Tam B, Chow S. A preliminary report on the effectiveness of Nanotechnology Anti-Microbial Spray Dressing in preventing tenckhoff Catheter Exit-Site Infection. *Periton Dialysis Int.* 2014; 34, 6
12. KA Wan, MY Ng, YT Wong. New horizon on community-acquired methicillin resistant *Staphylococcus aureus* (CA-MRSA) skin and soft tissue infection: nanotechnology antimicrobial spray. *Hong Kong j. emerg. Med.* 2011; 18(6): 432-436
13. Li W, Ma X, Peng Y, et al. Application of a nano-antimicrobial film to prevent ventilator-associated pneumonia: A pilot study. *Afr J Biotechnol.* 2011; 10(10): 1926-1931
14. Yuen J, Yung J. Medical implications of antimicrobial coating polymers- organosilicon quaternary ammonium chloride. *Mod Chem Appl.* 2013, 1:3
15. He W, Ye Z, Wang D. Application a nanotechnology antimicrobial spray to prevent lower urinary tract infection: a multi urology centers trial[J]. *J TRANSL MED.* 2012, 10(Suppl 1):S14
16. Marks LR, Reddinger RM, Hakansson AP. Biofilm formation enhances fomite survival of *Streptococcus pneumoniae* and *Streptococcus pyogenes*. *Infection and immunity* 2014;82:1141-6.
17. Yan J, Bassler BL. Surviving as a Community: Antibiotic Tolerance and Persistence in Bacterial Biofilms. *Cell Host Microbe.* 2019;26(1):15-21.
18. Razdan K, Garcia-Lara J, Sinha VR, Singh KK. Pharmaceutical

- strategies for the treatment of bacterial biofilms in chronic wounds. *Drug Discov Today*. 2022;27(8):2137-2150.
19. Lin Y, Chen J, Zhou X, Li Y. Inhibition of *Streptococcus mutans* biofilm formation by strategies targeting the metabolism of exopolysaccharides. *Crit Rev Microbiol*. 2021 Sep;47(5):667-677.
20. Lusardi G, Lipp A, Shaw C. Antibiotic prophylaxis for short-term catheter bladder drainage in adults. *The Cochrane database of systematic reviews* 2013;7:CD005428.
21. David J.S, Bacterial biofilms in patients with indwelling urinary catheters , *Nature Clinical Practice Urology* 2008,11(5):598-608

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