

Distribution and Drug Resistance of Pathogenic Bacteria in Diabetic Patients with Double J-Stent Associated Infections

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Objective: To analyze the distribution and drug resistance of pathogenic bacteria in diabetic patients with double J-stent associated infections, and to explore the strategies for prevention and treatment of the infections.

Methods: From January 2019 to December 2021, 266 diabetic patients treated with double J-stent placement in our hospital assessed for eligibility were recruited. Urine and double J-stent samples were collected for pathogenicity assay and screened for biofilm bacteria. Pathogenic bacteria distribution and drug resistance were examined.

Results: A total of 97 strains (36.5%) of pathogenic bacteria were isolated from urine samples and 129 strains (48.5%) from double J-stent samples ($P > 0.05$). 3 strains (1.1%) of biofilm bacteria were separated from urine samples and 106 strains (39.8%) from double J-stent samples ($P < 0.05$). In the double J-stent samples, there were significantly higher ratios of Gram-positive bacteria separated from biofilm bacteria versus the urine-cultured pathogens (44.3%/61.3%, $P < 0.05$), and higher drug resistance was observed in biofilm bacteria versus urine-cultured pathogens ($P < 0.05$). Fosfomycin tromethamine showed remarkable susceptibility to both urinary cultured pathogens and double J-stent biofilm bacteria.

Conclusion: Diabetic patients with double J-stent biofilm-positive bacteria are mainly Gram-positive bacteria, which are prone to biofilm formation and show strong drug resistance.

Keywords: pathogenic bacteria distribution, drug resistance, diabetic patients, double J-stent

Introduction

It has been reported that diabetic patients present a higher risk of urinary tract infections than healthy individuals, which may be owing to the following factors: ① The high glucose environment decreases the chemotaxis and phagocytosis of leukocytes, and disorders the body's immune system, resulting in a decreased ability of the body against infection. ② The poorly controlled blood sugar level increases the glucose level in the urine, facilitating the growth of bacteria. ③ The increase in urine sugars level provides a breeding ground for bacterial growth. ④ The misuse of antibiotics leads to dysbiosis.¹ The double J-stent placed in the patient's body provides a surface for bacteria adhesion, and the bacterial biofilm increases the risk of urinary tract infection in diabetic patients.² The biofilm is a three-dimensional membrane-like structure formed by bacteria that adheres to the surface of solid materials during their growth to adapt to the growth environment. Previous research has shown that diabetes mellitus is an independent high-risk factor of double J-stent peritonitis infection,³ but the double J-stent related infections in diabetic patients were marginally explored. To understand the pathogenic characteristics of urinary tract infections in diabetic patients after double J-stent placement, this study analyzed the pathogens including biofilm bacteria in the urine and double-J stent of 266 diabetic patients with double-J stent placement from January 2019 to December 2021 in Zigong First People's Hospital to provide a theoretical basis for clinical treatment. The results are as follows.

Materials and Methods

Materials

Clinical Data

Between January 2019 and December 2021, 266 diabetic patients with double J stent placement in our hospital were recruited after assessment for eligibility. Inclusion criteria: ① Patients aged 18–80 years old; ② with a clear diagnosis of type 2 diabetes mellitus; ③ double J-stent indwelling for not less than 7 d; ④ with COOK double J-stent of 5F – 7F diameter; ⑤ with a survival time of ≥ 6 months; ⑥ Good blood sugar control, glycosylated hemoglobin $\leq 6\%$. Exclusion criteria: ① Patients with urinary tract infection before double J-stent placement; ② with contraindications to double J-stent placement; ③ with failed double J-stent placement; ④ with postoperative infection from other causes or with obvious manifestations of systemic infection; ⑤ with other forms of urinary tract drainage (including catheterization, cystostomy, nephrostomy) 1 month before double J-stent removal; ⑥ Those who received antibacterial treatment within 1 month or necessary antibacterial treatment during double J tube placement. The study was approved by the hospital ethics committee (Ethics No. 20191043). Undersigned written informed consent form was obtained from all patients.

Baseline Data

The patient's age, gender, reasons for placement, and duration of stent placement were recorded.

Methods

Sample Collection and Bacteria Culture

With the patient in a lithotomy position, after routine disinfection, draping, and local anesthesia, clean intermittent catheterization was performed, followed by the collection of 3mL of urine using a disposable sterile syringe. The urine was then placed in a sterile bottle and sent to the microbiology room for bacterial identification. The double J-stent was removed under cystoscopy and washed repeatedly with saline. The double J stent was sectioned into approximately 2 cm sample segments and placed in inoculation bottles with 30 mL of saline and eluted for 1 min with a vortex shaker at 3000 R/min. The precipitates were inoculated in blood agar plate medium and MacConkey agar medium, placed in a constant temperature incubator at 37°C for 16–24 h and then observed for colony generation and strain and drug sensitivity identification.

Screening for Biofilm Bacteria

The black dried colonies appearing in Congo red agar are biofilm strains and the red colonies are planktonic. These black dried colonies were inoculated in a blood plate for overnight incubation, followed by strain and drug sensitivity identification.⁴

Bacterial Identification and Drug Sensitivity

Bacterial identification and drug sensitivity identification were performed using a fully automated Vitek 2 compact instrument from Mérieux, France, with reagents for GN and GP identification cards matched with GN13 and GP67 antimicrobial susceptibility testing cards.⁴ The drug sensitivity was determined for planktonic and biofilm bacteria as per the paper diffusion method recommended by the American Clinical Laboratory Standardization Institute (CLSI), and fosfomycin tromethamine was determined for Enterobacteriaceae and Enterococcaceae fold point criteria as per the fosfomycin criteria specified by CLSI.⁵

Results

Baseline Data of Patients

Patients' general information is presented in Table 1.

Detection of Pathogenic Bacteria in Urine and Double J-Stent Samples

A total of 266 strains of pathogenic bacteria were detected in 266 diabetic patients with double-J stent indwelling in urine culture and double-J stent, including 97 strains in urine (36.5%, 97/266) and 129 strains in double J stent (48.5%, 129/

Table 1 Baseline Data of Patients

Items	n	Ratio (%)
Age		
< 60 year	141	53.01
≥60 year	125	46.99
Gender		
Male	143	53.75
Female	123	46.25
Reason for placement		
Urinary stone surgery	178	66.92
Urinary stenosis (including UPJ)	31	11.65
Urinary tumor	8	3.01
Compression of the ureter caused by tumors outside the urinary system	12	4.51
Others	37	13.91
Abnormal serum creatinine		
Yes	161	60.53
No	105	39.47
Intubation time		
7~30d	47	17.67
30~60d	135	50.75
60~90d	49	18.42
≥90d	35	13.16

266) (36.5%/48.5%, $P > 0.05$). A total of 109 strains of biofilm bacteria were isolated, among which 3 strains (1.1%, 3/266) in urine and 106 strains (39.8%, 106/266) in double J-stent (1.1%/39.8%, $P < 0.05$) (Table 2).

The Distribution and Composition Ratios of Urinary Pathogenic Bacteria and Double J-Stent Biofilm Bacteria

A total of 97 pathogenic bacteria were identified in the fluid samples, including 54 Gram-negative bacteria (55.7%, 54/97) and 43 Gram-positive bacteria (44.3%, 43/97), and the detection rate of Gram-negative bacteria was higher than that of Gram-positive bacteria (55.7%/44.3%, $P > 0.05$). A total of 106 biofilm bacteria were isolated from the double J-stent samples, among which 41 (38.8%, 41/106) were Gram-negative and 65 (61.2%, 65/106) were Gram-positive, and the detection rate of Gram-positive bacteria was significantly higher than that of Gram-negative bacteria (38.8%/61.2%, $P < 0.05$) (Table 3).

Drug Resistance

The drug resistance of urinary pathogenic bacteria and double J-stent biofilm bacteria were presented in Tables 4 and 5.

Table 2 Detection of Pathogenic Bacteria in Samples

Samples	Bacterial Culture		Biofilm Bacteria Culture	
	Positive	Negative	Positive	Negative
Urine	97 (36.5%)	169	3 (1.1%)	263
Double J stent	129 (48.5%)	137	106 (39.8%)	160
χ^2	2.712		122.41	
P	0.09		<0.001	

Table 3 Distribution and Composition Ratio of Pathogenic Bacteria

Pathogenic Bacteria	Pathogenic Bacteria in Urine Culture		Double J-Stent Biofilm Bacteria	
	Strain	Composition Ratio (%)	Strain	Composition Ratio (%)
Gram-negative bacteria	54	55.7	41	38.7
Escherichia coli	25	25.8	17	16.0
Klebsiella pneumoniae	17	17.5	11	10.4
Acinetobacter baumannii	1	1.0	3	2.8
Enterobacter cloacae	8	8.3	6	5.7
P. Aeruginosa	3	3.1	4	3.8
Gram-positive bacteria	43	44.3	65	61.3
Staphylococcus aureus	16	16.5	27	25.5
Staphylococcus epidermidis	9	9.4	16	15.1
Staphylococcus haemolyticus	6	5.8	7	6.6
Enterococcus Faecium	7	7.3	8	7.5
Enterococcus faecalis	5	5.3	7	6.6
Total	97		106	

Table 4 Drug Resistance in Gram-Negative Bacteria

Antibacterial Drugs	Pathogenic Bacteria in Urine Culture		Double J-Stent Biofilm Bacteria		P
	Strain (55)	Ratio (%)	Strain (41)	Ratio (%)	
Fosfomycin tromethamine	5	9.1	5	12.2	0.644
Ampicillin	45	81.8	31	90.2	0.351
Ampicillin/Sulbactam	21	38.2	27	65.9	0.009
Piperacillin/tazobactam	3	5.5	6	14.6	0.134
Cefazolin	32	58.2	38	92.7	<0.001
Cefuroxime	28	50.9	32	78.0	0.008
Ceftazidime	19	34.5	25	61.0	0.125
Ceftriaxone	34	61.8	34	82.9	0.032
Cefepime	10	18.2	11	26.8	0.333
Cefotetan	2	3.6	3	7.3	0.434
Aztreonam	17	30.9	14	34.1	0.784
Ertapenem	0	0	4	9.7	0.019
Imipenem	4	7.3	7	17.0	0.144
Meropenem	3	5.5	9	22.0	0.017
Amikacin	9	16.4	11	26.8	0.228
Gentamicin	24	43.6	21	51.2	0.512
Tobramycin	8	14.5	16	39.0	0.007
Ciprofloxacin	21	38.2	40	97.5	<0.001
Levofloxacin	26	47.2	33	80.4	0.001
Trimethoprim/sulfamethoxazole	28	50.9	29	70.7	0.062
Nitrofurantoin	9	16.4	19	26.7	0.001

Susceptibility

The susceptibility of urinary pathogens and double J-stent biofilm bacteria to fosfomycin tromethamine was shown in [Table 6](#).

Discussion

Diabetic patients are at a high risk of urinary tract infections, which complicates the management of urinary tract infections, and delayed treatment may result in critical illnesses such as infectious shock. In this study, 97 strains of pathogenic bacteria

Table 5 Drug Resistance of Gram-Positive Bacteria

Antibacterial Drugs	Pathogenic Bacteria in Urine Culture		Double J-Stent Biofilm Bacteria		P
	Strain (55)	Ratio (%)	Strain (41)	Ratio (%)	
Fosfomycin Trometamol	3	7.0	4	7.1	0.974
Penicillin G	26	60.5	52	93.8	<0.001
Ampicillin	17	39.5	49	87.5	<0.001
Oxacillin	13	30.2	38	67.8	<0.001
HGEN	13	30.2	26	46.5	0.102
Gentamicin	12	27.9	31	55.4	0.006
HLSR	9	20.9	21	37.5	0.075
Rifampicin	0	0	14	25.0	<0.001
Ciprofloxacin	22	58.1	27	48.2	0.770
Levofloxacin	28	65.1	47	83.9	0.030
Moxifloxacin	21	48.8	34	60.7	0.238
Trimethoprim/sulfamethoxazole	15	34.9	30	53.6	0.064
Clindamycin	19	44.2	29	51.8	0.453
Erythromycin	19	44.2	27	48.2	0.690
Nitrofurantoin	8	18.6	27	65.9	0.002
Linezolid	0	0	9	16.1	0.005
Vancomycin	0	0	1	1.7	0.378
Quinupristin/Dalfopristin	0	0	3	5.3	0.123
Tetracycline	18	41.9	26	46.4	0.649
Tigecycline	0	0	3	5.3	0.123

Table 6 Durability of Common Pathogenic Bacteria to Fosfomycin Trometamolium

Pathogens	Pathogenic Bacteria in Urine Culture				Double J-Stent Biofilm Bacteria			
	Strain	Sensitivity	Medium	Resistance	Strain	Sensitivity	Medium	Resistance
Escherichia coli	23	19	3	1	17	11	5	1
Klebsiella pneumoniae	15	10	3	2	11	8	3	0
Enterobacter cloacae	7	4	3	0	6	3	3	0
Pseudomonas aeruginosa	3	1	1	1	4	1	1	2
Acinetobacter baumannii	1	0	0	1	3	0	1	2
Staphylococcus aureus	14	11	2	1	27	17	8	2
Staphylococcus epidermidis	8	6	2	0	16	11	4	1
Staphylococcus haemolyticus	5	4	1	0	7	5	2	0
Enterococcus faecium	6	3	2	1	8	4	3	1
Enterococcus faecalis	5	3	1	1	7	4	3	0
Total	97	62	21	8	106	64	33	9

were identified in the urine of 266 diabetic patients with indwelling double J-stent (36.5%, 97/266), mainly 54 strains (55.4%, 54/97) of gram-negative bacteria, among which *Escherichia coli* with 25 strains Gram-negative bacteria had high resistance to semi-synthetic penicillins (ampicillin resistance of 81.8%), first, second, and third-generation cephalosporins (eg cefazolin, cefuroxime, ceftazidime resistance of 58.2%, 50.9%, and 34.5%, respectively) and quinolones (levofloxacin resistance of 47.2%), but they were sensitive to antimicrobial drugs with β -lactamase inhibitors (5.5% for piperacillin/tazobactam), aminoglycosides (16.4% for amikacin), and extremely sensitive to carbapenems (ertapenem resistance of 0%). Gram-positive bacteria were also resistant to penicillins (penicillin G resistance of 60.51%) and quinolones (levofloxacin

resistance of 65.1%%), but highly sensitive to linezolid, vancomycin, and quinupristin/dalfopristin (vancomycin resistance of 0%). The results are broadly in line with other studies on the distribution and resistance of pathogenic bacteria in diabetic patients with urinary tract infections in recent years, but with a higher proportion of Gram-positive bacteria.^{6,7}

Pathogenic bacteria in urine exist mainly in the form of free bacteria (only 3 strains of biofilm bacteria were isolated from urine specimens in the present study), which fails to fully reflect the real situation of urinary tract infection in patients with indwelling double J-stent. In the absence of the normal protective mechanism of body tissues on the surface of a double J stent,⁴ bacteria can easily adhere to the stent and gradually form microcolonies and wrap around the surface by continuously secreting polysaccharide complexes such as polysaccharide, fibronectin, and lipopolysaccharide during double J stent placement.² Most relevant studies have revealed the most common pathogen of double J-stent biofilm bacterium to be *Escherichia coli*,^{2,4,8} which may be associated with its frequent presence in urinary tract infections and the highly adherent type I cilia on the surface of *Escherichia coli*.⁹ In the present study, 106 biofilm bacteria were finally isolated from double J-stent specimens, predominantly Gram-positive bacteria (61.3%, 65/106), in which *Staphylococcus aureus* was the most common, followed by *Staphylococcus epidermidis* infection, which differed from the results of previous studies on the biofilm bacteria of double J-stent and the rate of Gram-positive bacteria detected in the urine of the present study (43.7%/ 61.3%, $P < 0.05$). Presumably, this is attributed to the ability of staphylococci to produce polysaccharide mucilage that encourages adhesion of staphylococci to smooth surfaces and has an anti-phagocytic effect. Moreover, it may be related to high urine glucose in diabetic patients. According to Mack et al,¹⁰ a high glucose environment increased the production of Staphylococcal biofilm in vitro experiments, and animal experiments by Mack et al¹⁰ also demonstrated that a high glucose environment significantly promoted the multiplication of Staphylococci and the growth of bacteria. Nevertheless, the inspection of urinary glucose levels of the patients was absent in this study, and the correlation between the high urinary glucose environment and the formation of bacterial biofilm in double J-stent requires further investigation.

Previous studies have found more resistance in double J-stent biofilm bacteria than in urinary planktonic bacteria,^{2,8} which is attributed to the fact that the biofilm enveloping the double J-stent forms a physical barrier to the penetration of antibiotics and immune cells, and the concentration gradient of nutrients in the microenvironment causes deep bacteria to be in a “sub-hibernating” state with low metabolism. Such “sub-hibernating” bacteria are less susceptible to antibiotics and are prone to develop resistance, which can be transmitted between periplasmic bacteria through the bacterial population sensing system (QS).¹¹ Under the protection of the biofilm, the membranous bacteria can sufficiently multiply and acquire drug-resistant genes. Upon maturation of conditions, highly resistant biofilm bacteria re-disseminate into the urine, thereby eliciting a refractory urinary tract infection. The present study also showed that the drug resistance of double J-stent biofilm bacteria was generally higher than that of urine free bacteria, and a comparative analysis of the data from the two groups showed a statistically significant difference ($P < 0.05$). This poses a great challenge for the selection of clinical antimicrobial drugs.

The fosfomycin molecule can irreversibly bind to pyruvate-uracil diphosphate-acetylglucosaminyltransferase, interfering with the first step of bacterial cell wall mucopeptide synthesis and inhibiting the subsequent reaction, thereby exerting a bactericidal effect. Fosfomycin tromethamine is an oral form of fosfomycin (fosfomycin has a low intestinal absorption rate), and its advantages for the treatment of urinary tract infections include (1) single-dose oral use and high patient compliance, (2) unique mechanism of action and infrequent cross-resistance with other antibacterial drugs, and (3) higher urinary drug concentrations than those of other commonly used antibiotics (eg, cephalosporins, quinolones) and the effective bactericidal urinary drug concentrations lasting up to 48 hours.¹² Weng et al¹³ concluded, after MATA analysis of the effectiveness and safety of fosfomycin tromethamine in the treatment of urinary tract infections, that the efficacy of fosfomycin tromethamine in the treatment of complicated urinary tract infections is comparable to that of other antibiotics, with the significant advantage of the single oral dose, convenient dosing, and outstanding performance in safety. In a multicenter clinical trial in China, a dosing regimen of fosfomycin tromethamine dispersion 3 g orally once every other day for 3 doses was found to be effective in treating patients with non-febrile lower urinary tract infections caused by non-multidrug-resistant, multi-drug-resistant bacteria with mild adverse effects.¹⁴ In addition, a study by Wang et al¹⁵ in elderly patients with diabetes mellitus combined with acute urinary tract infections showed that a 1-week regimen of fosfomycin tromethamine dispersion with 3 g/day was effective in acute cystitis. The present study revealed good susceptibility to fosfomycin tromethamine in both urinary planktonic bacteria

and double J-stent biofilm bacteria. The overall resistance rate of urinary planktonic bacteria to fosfomycin tromethamine was 8.2% (8/97) and was only insensitive to *Acinetobacter baumannii* (due to the small sample size). Moreover, the overall resistance rate of double J-stent biofilm bacteria to fosfomycin tromethamine was 8.45% (9/106), with only *Acinetobacter baumannii* and *Pseudomonas aeruginosa* being insensitive. These all suggest the potential of fosfomycin tromethamine in the prevention and treatment of diabetic patients with double J-stent-related infections. However, it is worth considering that there are large structural differences between the biofilm strains observed in the present study and the actual bacterial biofilm in vivo, so the efficacy and safety of fosfomycin tromethamine in the treatment of diabetic patients with double J-stent associated infections need to be further explored.

Conclusion

Diabetic patients with double J-stent biofilm-positive bacteria are mainly Gram-positive bacteria, which are prone to biofilm formation and show strong drug resistance. However, its efficacy and safety require further investigation. The limited sample size of this study fails to exclude the possibility of chance (eg, geographical distribution differences). The relationship between double J-stent bacterial biofilm formation in a high urinary glucose environment and the presence of a specific inflammatory response and immune response to pathogenic bacteria in diabetic patients remains for exploration. In addition, this study has not yet explored the differences in bacterial infection of double J ducts in patients with different blood glucose control levels, and it is planned to be analyzed in future studies.

Data Sharing Statement

All data generated or analysed during this study are included in this published article.

Ethics Approval and Consent to Participate

This study has been approved by First People's Hospital of Zigong City ethics committee and Patients and their families were informed of the research content and voluntarily signed the informed consent. All the methods were carried out in accordance with the Declaration of Helsinki.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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