


**Original Article: Laboratory Investigation****Intraluminal diamond-like carbon coating with anti-adhesion and anti-biofilm effects for uropathogens: A novel technology applicable to urinary catheters**

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**Abbreviations & Acronyms**

3D = three-dimensional  
CFU = colony-forming unit  
CLSM = confocal laser scanning microscopy  
CVD = chemical vapor deposition  
DLC = diamond-like carbon  
GFP = green fluorescent protein  
OsO<sub>4</sub> = osmium tetroxide  
SEM = scanning electron microscope

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**Objectives:** To examine anti-adhesion and anti-biofilm effects of a diamond-like carbon coating deposited via a novel technique on the inner surface of a thin silicon tube.

**Methods:** Diamond-like carbon coatings were deposited into the lumen of a silicon tube with inner diameters of 2 mm. The surface of the diamond-like carbon was evaluated using physicochemical methods. We used three clinical isolates including green fluorescent protein-expressing *Pseudomonas aeruginosa*, *Escherichia coli* and *Staphylococcus aureus*. We employed a continuous flow system for evaluation of both bacterial adhesion and biofilm formation. Bacterial adhesion assays consisted of counting the number of colony-forming units and visualization of adhered bacterial cells by scanning electron microscope to evaluate the diamond-like carbon-coated/uncoated samples. The biofilm structure was analyzed by confocal laser scanning microscopy on days 3, 5, 7 and 14 for green fluorescent protein-expressing *Pseudomonas aeruginosa*.

**Results:** The smooth and carbon-rich structure of the intraluminal diamond-like carbon film remained unchanged after the experiments. The numbers of colony-forming units suggested lower adherence of green fluorescent protein-expressing *Pseudomonas aeruginosa* and *Escherichia coli* in the diamond-like carbon-coated samples compared with the uncoated samples. The scanning electron microscope images showed adhered green fluorescent protein-expressing *Pseudomonas aeruginosa* cells without formation of microcolonies on the diamond-like carbon-coated samples. Finally, biofilm formation on the diamond-like carbon-coated samples was lower until at least day 14 compared with the uncoated samples.

**Conclusions:** Intraluminal diamond-like carbon coating on a silicone tube has anti-adhesion and anti-biofilm effects. This technology can be applied to urinary catheters made from various materials.

**Key words:** bacterial adhesion, biofilms, plasma gases, urinary catheters, urinary tract infection.

**Introduction**

Urinary catheters are used worldwide in the field of urology.<sup>1</sup> However, bacteriuria develops in almost 100% of people within 30 days of urinary catheter insertion.<sup>2</sup> Bacteria in the urine adhere to and colonize on the catheter surface, which results in rapid biofilm formation, followed by catheter obstruction and symptomatic urinary tract infection.<sup>3</sup> Various catheters and materials<sup>4–7</sup> have been developed over the years; however, none have provided completely satisfactory clinical outcomes. Silicone catheters are the most widely used for long-term indwelling.<sup>1</sup>

DLC is an amorphous hard film composed of carbon allotropes. DLC coating, deposited in the Radio Frequency plasma CVD system, was reported to consist of a hydrogenated amorphous carbon type, involving hybrid carbon-carbon bonds of sp<sup>3</sup> and sp<sup>2</sup>.<sup>8</sup> DLC coatings are considered suitable for application in medical devices because of their biocompatibility along

with a number of other useful properties, including low friction, smoothness, abrasion resistance and low cost.<sup>9,10</sup> A previous report showed that DLC deposited onto a polyurethane film reduced bacterial adhesion and encrustation.<sup>11</sup> Despite these promising reports, DLC coatings have not been applied for use in urinary catheters, owing to technical limitations associated with application of DLC coatings into the lumen of small-diameter tubes; DLC coatings were only previously demonstrated on flat surfaces using conventional methods. In 2018, however, Nakatani *et al.*<sup>12</sup> developed the world's first technique for DLC coating on the inner surface of a thin tube. As bacterial biofilms are known to develop more in the lumen than on the outer surface of tubular medical devices,<sup>13</sup> coatings exhibiting anti-adhesion and anti-biofilm effects should be applied to the lumen. Therefore, the novel technique for DLC coating developed by Nakatani *et al.* was expected to offer utility for use in urinary catheters.

In the present study, we examined the properties of DLC coating deposited (via a novel technique) on the inner surface of a thin silicon tube. Anti-adhesion and anti-biofilm effects, as well as physicochemical and biological properties were evaluated, and compared to those of an uncoated silicon tube.

## Methods

### DLC coating

A silicon tube with inner and outer diameters of 2 and 3 mm, respectively (LABORAN<sup>®</sup>; AS ONE Corporation, Osaka, Japan), was used to demonstrate luminal DLC coating. The silicon tube was first washed with ethylene in preparation for coating. The coating process was then performed in the chamber using the AC high-voltage methane plasma-enhanced CVD method.<sup>12</sup> The physicochemical properties of the DLC-coated/uncoated silicon surface were evaluated by 3D non-contact surface scanning using a New View 5320 (Zygo Corporation, Middlefield, OH, USA) and by scanning electron microscopy using a HITACHI S-4800 (Hitachi High-Tech Corporation, Tokyo, Japan). The surface morphology of DLC-coated/uncoated silicon was visualized with the SEM before and after the bacterial experiments. In addition, the proportions of surface elements on DLC-coated/uncoated silicon were measured by the energy dispersive X-ray spectroscopy method using a HITACHI S-4800, and corrected by the ZAF method.

DLC-coated/uncoated silicon tubes were cut into 10-cm samples and used in the experiments assessing both bacterial adhesion and biofilm formation after ethylene oxide gas sterilization.

### Bacterial strains and culture conditions

We used three clinical isolates with high capacity for biofilm formation including *Pseudomonas aeruginosa* OP14-210,<sup>14</sup> *Escherichia coli* OE-128 and *Staphylococcus aureus* OS-3, which were isolated from urinary tract infections at Okayama University hospital. pMF230, which is a broad-host-range plasmid for constitutive overexpression of GFP was a gift from Dr Michael J. Franklin (Montana State University).<sup>15</sup> To obtain a GFP-expressing *P. aeruginosa* strain OP14-210 (GFP-expressing *P. aeruginosa*), this strain was transformed with pMF230 by electroporation.<sup>16</sup>

These strains from frozen stocks were grown on tryptsoya broth (Nissui, Tokyo, Japan) containing 1.5% agar at 37°C. After growth overnight, a single colony from each plate was picked and used as bacterial inoculum in tryptsoya broth with carbenicillin at 300 µg/mL for GFP-expressing *P. aeruginosa* or without antimicrobial agents for *E. coli* and *S. aureus*, and grown overnight at 37°C with shaking.

### Continuous flow system

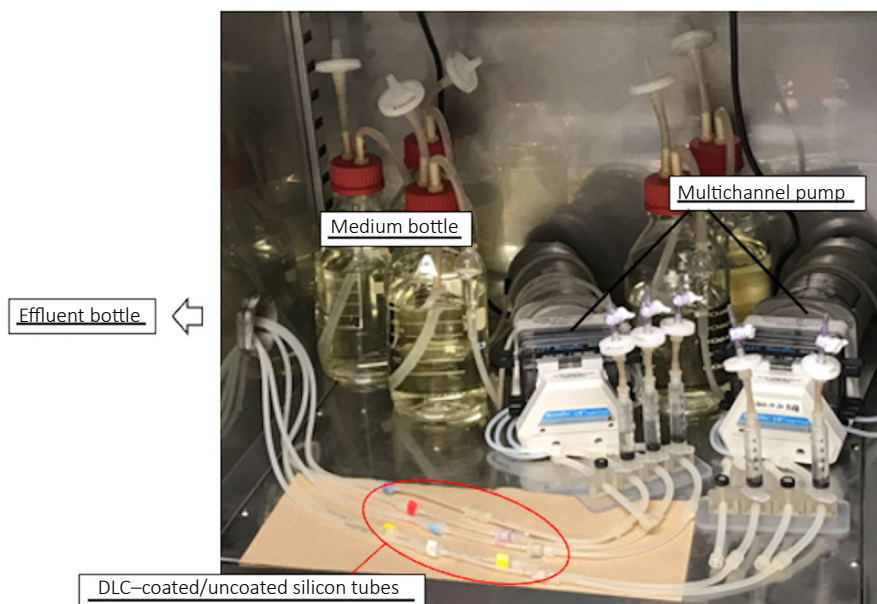
The flow system described by Sanchez *et al.*<sup>17</sup> was modified for evaluation of both bacterial adhesion and biofilm formation. First, the samples were connected to a multichannel pump (IPC8; ISMATEC, Wertheim, Germany) in parallel, and filled with sterile modified artificial urine supplied by the pump from the medium bottle. Then, the inoculum cultures of each bacterial strain grown as described above were injected into the lumen of DLC-coated/uncoated samples. The samples were clamped and incubated for 2 h to allow the bacterial strains to adhere to the inner surface substratum. After 2 h, sterile modified artificial urine was continuously supplied at a flow rate of 20 mL/h by a pump at 37°C. After 10 min, which was sufficient time to wash away the planktonic bacteria and bacteria that reversibly adhered to the surface, we evaluated the bacteria that adhered irreversibly to the inner surface of the samples using bacterial adhesion assays. For the biofilm formation experiments, sterile modified artificial urine was continuously supplied into the lumen throughout the course of the experiments.<sup>18</sup> The GFP of *P. aeruginosa* OP14-210 (pMF230) was expressed in the modified artificial urine,<sup>14,18</sup> without carbenicillin, for at least 30 days. The continuous flow system is shown in Figure 1.

### Bacterial adhesion assays

The bacterial adhesion assays consisted of counting the number of CFUs and visualization of adhered bacterial cells using the SEM in the DLC-coated/uncoated samples.

For CFU counting, each rinsed sample, cut into fragments of 1 cm, was placed into 1.5-mL microcentrifuge tubes containing 1 mL sterile saline. The fragments with bacteria were then vigorously vortexed. The suspended bacterial cells were then serially diluted 10-fold in sterile saline, and 50 µL aliquots of each dilution were spread on Mueller-Hinton agar plates (Becton Dickinson, Sparks, NV, USA). After overnight incubation at 37°C, CFUs per fragment (mL) were determined using the following formula: CFUs × dilution magnification × 20. We used three strains including GFP-expressing *P. aeruginosa*, *E. coli* and *S. aureus* for CFU counting, while a total of 15 fragments per strain were evaluated in three independent experiments.

For SEM visualization using a HITACHI S-4800 device, the samples were fixed with 2% glutaraldehyde and 2% paraformaldehyde in phosphate-buffered saline overnight at 4°C, postfixed in 1% OsO<sub>4</sub>, and dehydrated via an ethanol series. The samples were critically dried, cut in half in the sagittal direction, mounted on stubs in the direction where the lumen could be observed, and deposited in OsO<sub>4</sub>. Stubs were mounted in the SEM to obtain micrographs.



**Fig. 1** Continuous flow system. This continuous flow system was constructed in the incubator to maintain 37°C.

## CLSM

To assess biofilm formation, microscopic observations and image acquisitions were performed by CLSM as reported by Sanchez *et al.*<sup>17</sup> We used a Zeiss LSM 780 (Carl Zeiss Co., Ltd, Oberkochen, Germany) on days 3, 5, 7 and 14 after bacterial inoculation into the samples, which were sufficiently long for the biofilm to mature.<sup>19</sup> 3D images and optical z-sections were generated using LSM ZEN-software (Carl Zeiss Co., Ltd). Three image stacks were acquired from each sample at 1- $\mu\text{m}$  intervals in z-section from the substratum to the top of the biofilm. Three independent experiments were performed according to the same protocol described above. In total, nine image stacks were acquired and analyzed for each DLC-coated/uncoated sample.

## Structural analysis of the biofilm

CLSM images were reconstructed and analyzed quantitatively using the COMSTAT software ver. 2.1.<sup>20</sup> Multiple images obtained at different depths of the biofilm were collected as z-stacks by 3D reconstruction and consisted of a series of

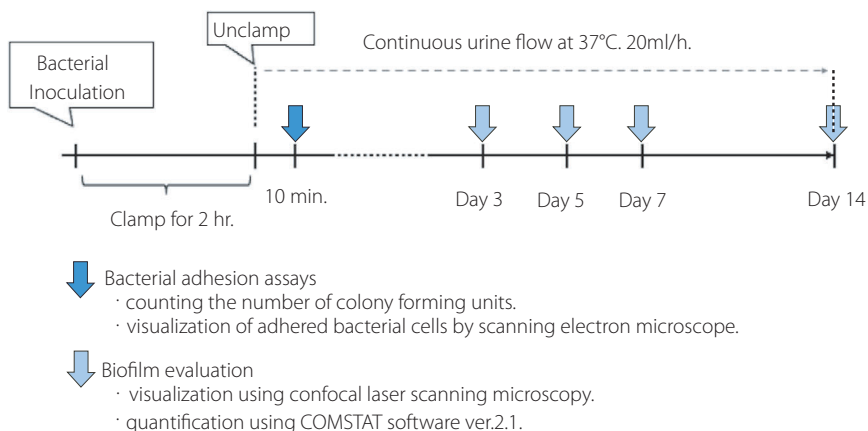
images with 1- $\mu\text{m}$  intervals in the z-section. Automatic thresholding and connected volume filtering were used for all image stacks. Quantification of image stacks was based on biomass and average biofilm thickness. The schedule of bacterial experiments including bacterial adhesion assay and biofilm evaluation was demonstrated in Figure 2.

## Statistical analysis

All data were analyzed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan).<sup>21</sup> Differences in the number of CFUs, biomass and average biofilm thickness between DLC-coated/uncoated samples were evaluated using a paired *t*-test. All *P* values were two-sided; a *P* value < 0.05 was taken to indicate statistical significance.

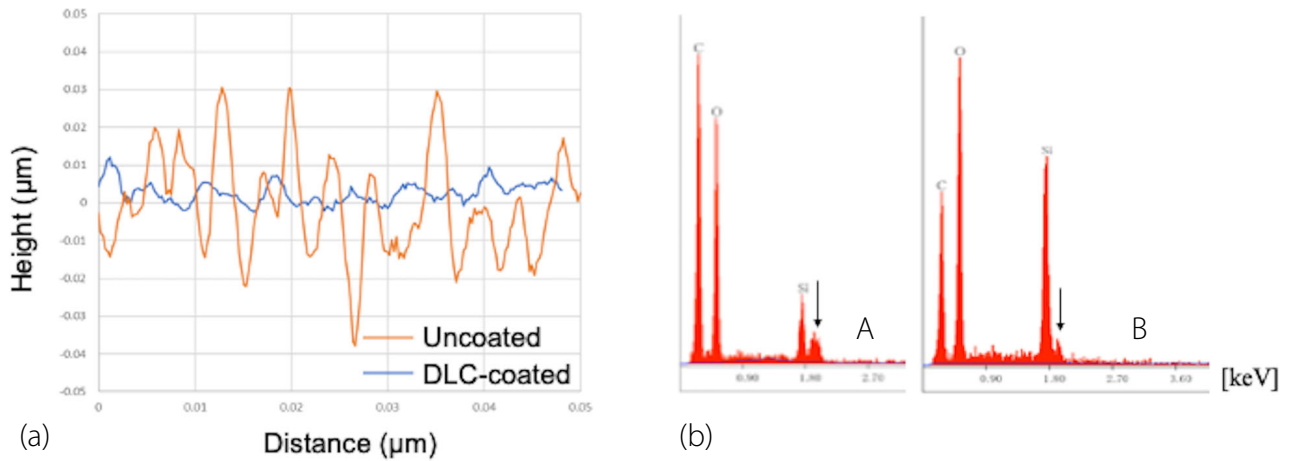
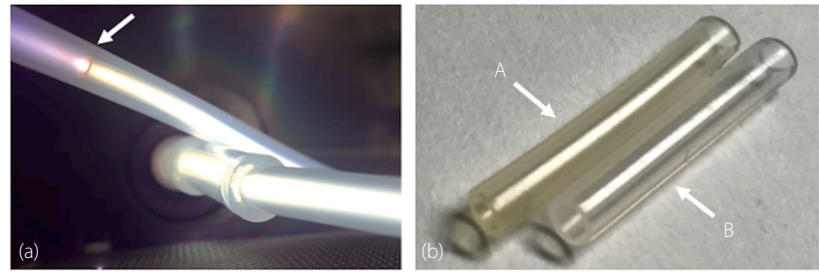
## Results

We observed DLC deposition in the lumen of the silicon tubes in the vacuum chamber (Fig. 3a,b). The DLC-coated surface showed improvements in smoothness and a high proportion of carbon content (Fig. 4a,b). According to the SEM



**Fig. 2** The schedule of bacterial experiments.

**Fig. 3** DLC coating. (a) DLC deposition on the luminal surface in the vacuum chamber. The silicon tube was loaded into the sheath tube. The arrow shows the tip of the silicon tube. Plasma emission throughout the lumen was confirmed, indicating DLC deposition. (b) Pictures of silicon tubes. The DLC coating made the silicon transparent and dark-yellow in color. A, DLC-coated silicon tube. B, uncoated silicon tube.

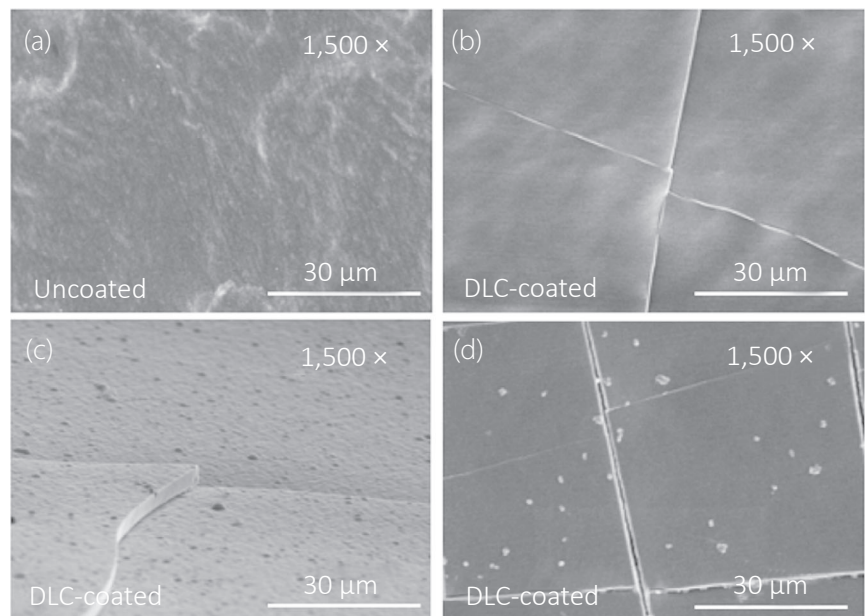


**Fig. 4** Physicochemical analysis. (a) Roughness (Ra) results measured using a New View 5320. The DLC-coated surface exhibited a 70% decrease in mean Ra value relative to the uncoated silicon surface. (b) Proportions of elements on the silicon surface. Proportions of surface elements as determined by the EDX method and corrected by the ZAF method using a HITACHI S-4800. The proportion of carbon increased on the DLC-coated surface (A) relative to the uncoated surface (B). The arrow indicates the osmium peak. C: carbon, O: oxygen, Si: silicon.

images, the surface of the uncoated silicone was uniformly rough (Fig. 5a), whereas a film-like thin structure with fissures could be observed on the surface of the DLC-coated silicon (Fig. 5b,c). The thin film retained its structure even after long-term exposure to artificial urine and bacteria for 2

months (Fig. 5d). The coating was also sufficiently flexible that it did not delaminate under external force including bending and friction of the catheter.

With regard to the CFU counting, the paired *t*-test showed that the mean number of CFUs in the DLC-coated fragments

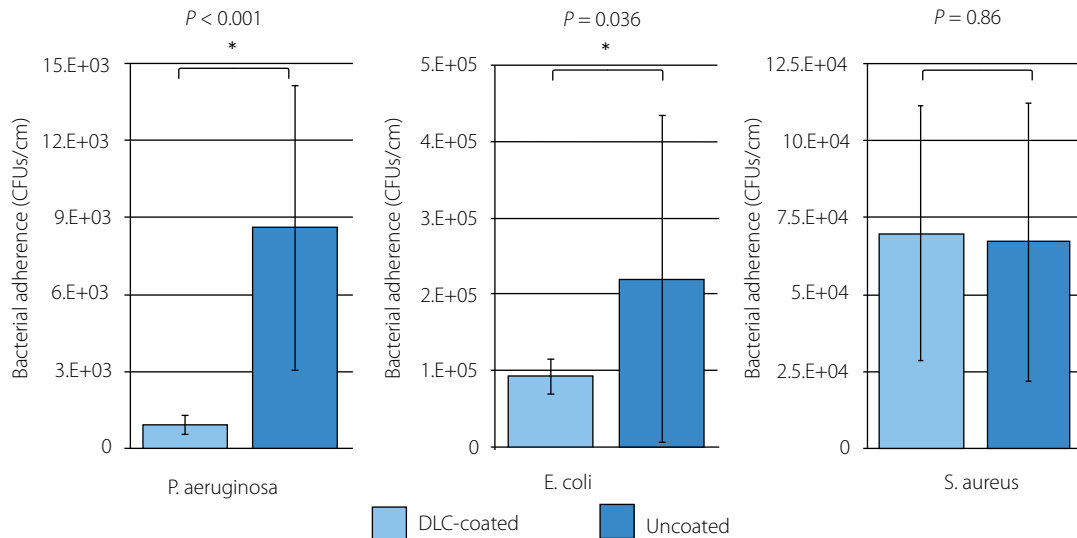


**Fig. 5** SEM visualization of intraluminal surface structures. All images were acquired at 1500 $\times$  magnification and accelerating voltage of 5.0 kV. (a) Uncoated silicon surface, vertical direction. (b) DLC-coated silicon surface, vertical direction. (c) DLC-coated silicon surface, horizontal direction. Deposition of a DLC layer approximately 3  $\mu$ m in thickness was confirmed. (d) Surface structure of DLC exposed to artificial urine and bacteria following the experiments, and visualized after removing the adhered cells on the surface with hydrochloric acid.

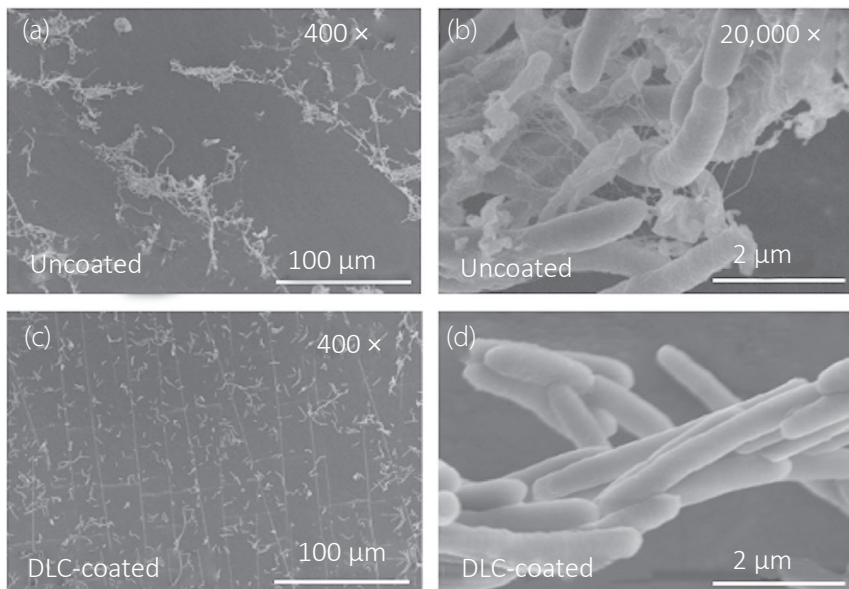


was significantly lower than in the uncoated fragments for GFP-expressing *P. aeruginosa* ( $9.2 \times 10^2$  vs  $8.6 \times 10^3$ ,  $P < 0.001$ ) and *E. coli* ( $9.2 \times 10^5$  vs  $2.2 \times 10^6$ ,  $P = 0.036$ ), respectively. In contrast, there was no statistical difference in CFU count between DLC-coated and uncoated fragments for *S. aureus* (Fig. 6). Using the SEM, we observed GFP-expressing *P. aeruginosa* cells adhered on the inner surface of the DLC-coated/uncoated samples. GFP-expressing *P. aeruginosa* were clustered together and formed some microcolonies with the glycocalyx, connecting cells together on the inner surface of the uncoated samples (Fig. 7a,b). In contrast, GFP-expressing *P. aeruginosa* cells were found to spread apart from each other without any extracellular structure on the inner surface of DLC-coated samples (Fig. 7c,d).

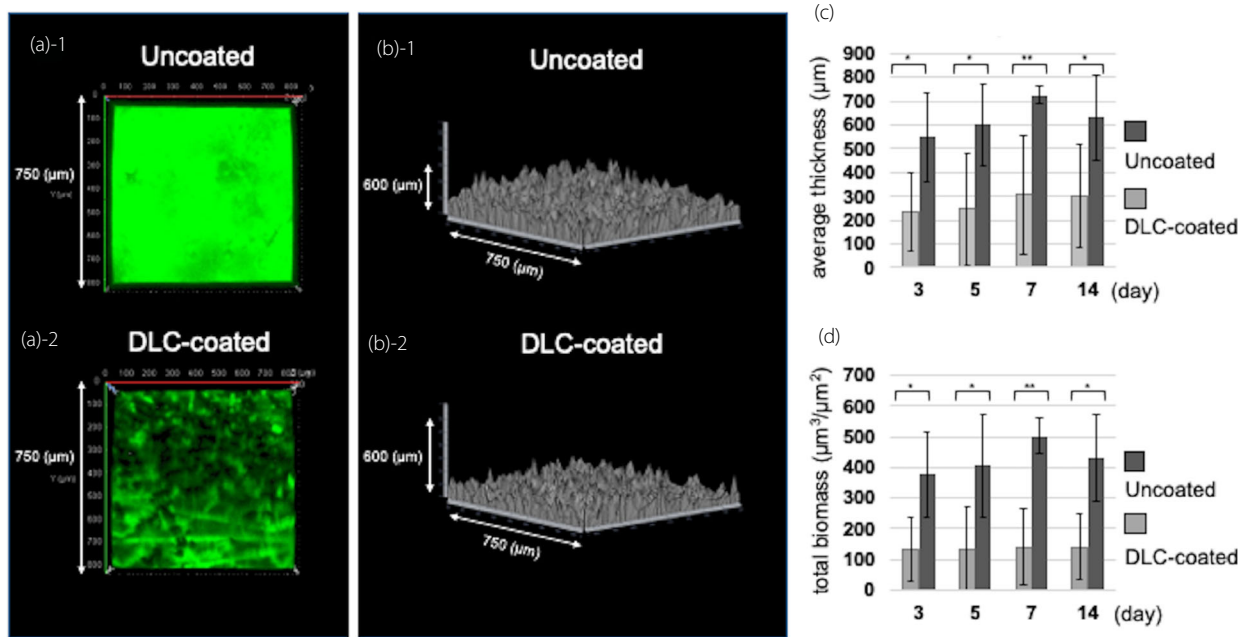
Visualization by CLSM, as well as 3D analyses, showed that GFP-expressing *P. aeruginosa* developed a biofilm on the inner surface of the uncoated silicon sample, with the whole surface covered on day 3 (Fig. 8a-1). Meanwhile, GFP-expressing *P. aeruginosa* developed an uneven biofilm with deficient areas on the inner surface of the DLC-coated silicon sample (Fig. 8a-2). In addition, visualization by CLSM, as well as 2.5-dimensional analyses, showed that the biofilms that developed on the uncoated silicon samples were larger than those on the DLC-coated samples (Figs 8b-1,b-2). Using the COMSTAT program, both biomass and average biofilm thickness were lower for the DLC-coated samples compared to the uncoated samples on days 3, 5, 7 and 14 (Fig. 8c,d). Based on a paired *t*-test, both biomass and average biofilm



**Fig. 6** Analysis of CFU counts. The number of CFUs (CFUs/cm) of bacteria irreversibly adhered on the inner surface of the DLC-coated/uncoated silicon fragments for *P. aeruginosa* OP14-210 (pMF230), *E. coli* OE-128 and *S. aureus* OS-3 were evaluated. Fifteen fragments per strain were evaluated in three independent experiments. *P* values were obtained using a paired *t*-test. Values represent the mean  $\pm$  SD.



**Fig. 7** SEM visualization of adhered *P. aeruginosa* OP14-210 (pMF230) cells. Visualization of adhered GFP-expressing *P. aeruginosa* cells on the inner surface of the samples 2 h after inoculum injection. All images were acquired at accelerating voltage of 5.0 kV. (a) Uncoated, 400 $\times$ . (b) Uncoated, 20,000 $\times$ . (c) DLC-coated, 400 $\times$ . (d) DLC-coated, 20,000 $\times$ .



**Fig. 8** Analysis of biofilm formation by *P. aeruginosa* OP14-210 (pMF230). (a, b) Images visualized with a Zeiss LSM780 and reconstructed using LSM ZEN software on day 3. All images were taken on a 750 μm × 750 μm square section. (a) Three-dimensional image. (a-1) Uncoated. (a-2) DLC-coated. (b) 2.5-dimensional image. (b-1) Uncoated. (b-2) DLC-coated. (c, d) Comparison of the biofilm quantified by reconstructed CLSM images using the COMSTAT software. (c) Average thickness. (d) Total biomass. Values represent the mean ± SD of nine image stacks acquired in three independent experiments. *P* values were obtained using a paired *t*-test. \**P* < 0.05, \*\**P* < 0.001.

thickness were lower in the DLC-coated silicon samples than in the uncoated samples, with statistically significant differences on days 3, 5, 7 and 14. Visualization of the bacteria-free samples (controls) by CLSM indicated that neither contamination nor biofilm formation could be observed after the conclusion of the experiments.

## Discussion

The results of the present study demonstrate the successful deposition of a DLC coating onto the inner surface of a thin silicon tube. A carbon-rich and smooth layer was observed following use of a novel DLC-coating technique, while the structure of the resultant DLC film remained unchanged throughout the course of the experiments. Moreover, the numbers of CFUs suggested less adherence of GFP-expressing *P. aeruginosa* and *E. coli* onto the DLC-coated silicon fragments compared with the uncoated fragments. SEM images of GFP-expressing *P. aeruginosa* cells showed adhered bacteria without formation of microcolonies on the inner surface of the DLC-coated sample, while CLSM images showed less biofilm formation on the DLC-coated samples until at least day 14, compared with the uncoated samples.

A clinical study using ureteral stents with a DLC coating only on the outer surface demonstrated that the DLC-coated stents enabled less painful and easier procedures compared with the stents that the patients had previously experienced, while cystoscopy showed no encrustation and biofilm on the outer wall of the DLC-coated stent during long-term indwelling.<sup>22</sup> However, the conventional method of coating deposition on only the outer surface of the stent might not prevent

lumen obstruction. DLC-coated stents would be expected to become even more effective with DLC deposition on both the outer wall and inner luminal surface. Using our novel intraluminal DLC deposition method, we were able to apply the coating to the inner surface of thin urinary catheters made not only of silicon but also of other materials, such as latex rubber.

CFU counting in the present study demonstrated that the DLC coating reduced the numbers of GFP-expressing *P. aeruginosa* and *E. coli* cells irreversibly adhering to the surface. These strains are highly pathogenic in the urinary tract; *E. coli* is the most common cause of urinary tract infections and *P. aeruginosa* is the main cause of biofilm formation on urinary catheters.<sup>23,24</sup> This result is consistent with previous studies reporting that improved smoothness of the surface structure reduced bacterial adhesion.<sup>11,25,26</sup> The DLC coating was likely effective at preventing bacterial colonization in the urinary tract, as it was found to strongly reduce adhesion of these gram-negative bacilli. The DLC coating did not inhibit adhesion for *S. aureus*. Inconsistency of results among the bacterial strains is probably based on the differentiation of mechanisms in which gram-positive and gram-negative bacteria adhere to surfaces; i.e. via matrix molecules in gram-positive bacteria and via pili in gram-negative bacteria.<sup>19,27,28</sup> However, gram-positive pathogens including *S. aureus* are a rare cause of catheter-associated urinary tract infections.<sup>23</sup>

*P. aeruginosa* is one of the most prevalent biofilm-forming bacteria in the urinary tract. Irreversible adherence of planktonic *P. aeruginosa* develops within 2 h of initial adhering, and the bacteria subsequently huddle together to form microcolonies.<sup>19</sup> Microcolony formation is an important initial step

in biofilm development. The thickness of the *P. aeruginosa* microcolony then increases, activating quorum-sensing-regulated genes, and finally resulting in the development of a mature biofilm within 9–12 days.<sup>19</sup> In the present study, SEM images showed that GFP-expressing *P. aeruginosa* adhered to the DLC did not form microcolonies even when the cells were in close proximity to each other. These results could be explained by the possibility that DLC coating prevented the migration and gathering of *P. aeruginosa*, known as twitching motility.<sup>29</sup> Finally, the DLC coating was found to be effective at inhibiting GFP-expressing *P. aeruginosa* biofilm formation until day 14. The results of our physicochemical experiments suggest that the smoothness and non-corrosiveness of the DLC coating ensured its anti-biofilm effects in the urine over a prolonged period of time. Furthermore, the high carbon content of the DLC coating may also have contributed to inhibition of biofilm formation, which is supported by the previous report.<sup>30</sup>

This study had several limitations. First, the three specific strains selected were validated only using a silicone tube and a modified artificial urine within an intraluminal continuous flow system. The physicochemical properties of the outer surface of the DLC-coated catheter as well as anti-adhesion and anti-biofilm effects were also need to be evaluated using other materials and strains. Second, the mechanism by which DLC inhibited biofilm formation was unclear. Bacterial adhesion assays using GFP-expressing *P. aeruginosa* provided a partial explanation for the mechanism of DLC anti-biofilm effects, but further studies should be conducted. Third, experiments focusing on encrustation, which is just as important as biofilm formation, have not yet been performed. To evaluate the DLC effects with regard to encrustation and the bacteria involved, further studies including *in vivo* experiments should be performed, preferably over a 14-day period. However, DLC coating would be expected to greatly reduce the crystalline bacterial biofilm formation according to previous studies.<sup>11,22,23</sup>

The intraluminal DLC coating, deposited on a silicone tube using a novel technique, demonstrated both anti-adhesion and anti-biofilm effects. This technology can be applied to urinary catheters constructed from various materials and “fully” DLC-coated catheters would be expected to exhibit a high degree of utility with less bacterial adherence and subsequent anti-biofilm effects for prolonged periods of time.

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## Conflict of interest

None declared.

## Author contributions

S. Watari: Protocol development, data collection, data analysis, manuscript writing. K. Wada: Protocol and project development, data management, data analysis, manuscript editing. M. Araki: Project development, data analysis, manuscript editing. T. Sadahira: Data management, manuscript editing. D. Ousaka: Project development, data collection. S. Ozawa: Project development, manuscript editing. T. Nakatani: Project development, data analysis, manuscript editing. Y. Imai: Data collection, data analysis. J. Kato: Data management, manuscript writing. R. Kariyama: Data management, manuscript editing. T. Watanabe: Data analysis, manuscript editing. Y. Nasu: Project development, manuscript editing.

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## Editorial Comment

### Editorial Comment to Intraluminal diamond-like carbon coating with anti-adhesion and anti-biofilm effects for uropathogens: A novel technology applicable to urinary catheters

Various techniques have been tried for coating the surface of an indwelling urethral catheter so as to reduce the frequency of bacteriuria, as well as catheter-associated urinary tract infections (CAUTI), resulting in so-called “antiseptic-coated catheters.” Several reports have been presented regarding such catheters coated with a silver alloy, which is known to have the best antibacterial activity among noble metals. In a meta-analysis that compared the frequency of asymptomatic bacteriuria between short-term use of silver alloy-coated and standard catheters, patients with a silver alloy-coated catheter had a significantly lower frequency of asymptomatic bacteriuria.<sup>1</sup> Also, a more recent report showed the usefulness of catheters coated with a noble metal, such as gold, silver or palladium.<sup>2</sup> As silver alloy-coated catheters are more expensive than non-coated catheters, cost-effectiveness has also been investigated. In a 12-month randomized cross-over trial, the rates of nosocomial CAUTI were compared between patients with silver-coated and uncoated catheters, and a hospital cost analysis was also carried out.<sup>3</sup> The findings showed that total catheter-related costs were reduced by 3.3–35.5% in cases that used a silver-coated type.

Pickard *et al.* carried out a multicenter randomized controlled trial with symptomatic urinary tract infection as the primary outcome.<sup>4</sup> The enrolled patients were considered to require short-term ( $\leq 14$  days) catheterization, and were divided equally into nitrofurantoin-impregnated, silver alloy and standard catheter groups. The incidence of symptomatic antibiotic-treated UTI in those three groups was 10.6%, 12.5% and 12.6%, respectively, whereas the use of a nitrofurantoin-impregnated catheter was found to be associated with a reduction in the incidence of symptomatic CAUTI. In contrast, nitrofurantoin-impregnated catheters, also referred to as antimicrobial-impregnated catheters, have been reported to be the most uncomfortable, compared with others, and are not available in Japan.

The present study reports reduced biofilm formation by the use of a urethral catheter with coating on the surface of the

lumen.<sup>5</sup> The findings are important, as this is one of only a few such studies carried out in Japan. However, as in previous reports, efficacy assessment was carried out over a relatively short period of 14 days. We are hopeful that efficacy over a period longer than 14 days will be investigated in the future. Furthermore, bacteria in urine is inevitable in patients with extended use of an indwelling urethral catheter, and CAUTI cannot be prevented only by catheter coating, thus, proper use of urethral catheters is most important.

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## Conflict of interest

None declared.

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