In Vitro Study of Antimicrobial Percutaneous Nephrostomy Catheters for Prevention of Renal Infections

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ABSTRACT Percutaneous nephrostomy (PCN) catheters are the primary method for draining ureters obstructed by malignancy and preventing a decline of renal function. However, PCN catheter-related infections, such as pyelonephritis and urosepsis, remain a significant concern. Currently, no antimicrobial PCN catheters are available for preventing infection complications. Vascular catheters impregnated with minocycline-rifampin (M/R) and M/R with chlorhexidine coating (M/R plus CHD) have previously demonstrated antimicrobial activity. Therefore, in this study, we examined whether these combinations could be applied to PCN catheters and effectively inhibit biofilm formation by common uropathogens. An *in vitro* biofilm colonization model was used to assess the antimicrobial efficacy of M/R and M/R-plus-CHD PCN catheters against nine common multidrug-resistant Gram-positive and Gram-negative uropathogens as well as *Candida glabrata* and *Candida albicans*. Experimental catheters were also assessed for durability of antimicrobial activity for up to 3 weeks. PCN catheters coated with M/R plus CHD completely inhibited biofilm formation for up to 3 weeks for all the organisms tested. The reduction in colonization compared to uncoated PCN catheters was significant for all Gram-positive, Gram-negative, and fungal organisms ($P < 0.05$). M/R-plus-CHD PCN catheters also produced significant reductions in biofilm colonization relative to M/R PCN catheters for *Enterobacter* spp., *Escherichia coli*, *Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, *C. glabrata*, and *C. albicans* ($P < 0.05$). M/R-plus-CHD PCN catheters proved to be highly efficacious in preventing biofilm colonization when exposed to multidrug-resistant pathogens common in PCN catheter-associated pyelonephritis. M/R-plus-CHD PCN catheters warrant evaluation in a clinical setting to assess their ability to prevent clinically relevant nephrostomy infections.

KEYWORDS nephrostomy, obstructed urethra, percutaneous nephrostomy catheter, catheter-related infection, pyelonephritis

Drainage catheters have become essential devices for patients with malignant or benign ureteral obstruction. Percutaneous nephrostomy (PCN) catheters are the primary method for draining obstructed ureters and prevention of acute renal failure in high-risk patients, such as those with cancer (1, 2). However, PCN catheters can be associated with infection complications, such as pyelonephritis, which have the potential to progress to urosepsis (3). The complications are often compounded by the immunosuppressive state resulting from advanced malignancy and subsequent systemic treatment (4). Several studies have reported an incidence of urinary tract infection (UTI) up to 20% (5) and PCN catheter-related incidence of pyelonephritis of 19% (2). Sepsis has been reported in 1.3% to 1.8% of patients with PCN catheters (3).

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Pathogenesis of nephrostomy tube-related infections begins with the colonization of the outer and/or luminal surfaces of PCN catheters by microbial biofilms, potentially progressing to a clinical infection (6). Skin flora contamination can occur early after placement, with bacterial organisms invading the insertion site, the urinary tract, and the new device. Moreover, since the obstructed system is often infected, a recently placed PCN catheter can be rapidly colonized with uropathogens infecting the renal pelvis and the upper portions of the ureter and could play a role in perpetuating the infection (3). Biofilms formed on implanted foreign-body surfaces, such as PCN catheters, can be especially recalcitrant to systemic antibiotic treatments, since many antibiotics are unable to penetrate the protective exopolysaccharide matrix formed by microbial biofilms on plastic surfaces (7). Minocycline-rifampin (M/R)-impregnated central venous catheters (CVCs) have demonstrated reduction in catheter-related bloodstream infections for patients with indwelling CVCs for vascular access (8–12). Further, CVCs coated with M/R and chlorhexidine (CHD) have demonstrated enhanced effectiveness *in vitro* in completely preventing biofilm colonization of vascular catheters by resistant bacteria and fungal organisms (13, 14). The purpose of this study was to examine whether these combinations of antimicrobial agents could be applied to PCN catheters and effectively inhibit microbial colonization of the devices by uropathogens. M/R CHD coating can potentially reduce nephrostomy infections, especially in immunocompromised cancer patients, who are at higher risk of developing pyelonephritis associated with neutropenia (2). An *in vitro* model was used to assess the prevention of biofilm colonization by key Gram-positive, Gram-negative, and fungal pathogens. We evaluated the antimicrobial activity and durability of M/R-plus-CHD nephrostomy catheters. The broad spectrum of microorganisms used in this study are implicated in pyelonephritis infections occurring in critically ill patients (2).

RESULTS

Baseline antimicrobial efficacy. The antimicrobial efficacy of M/R-plus-CHD PCN catheters was compared to that of M/R and uncoated control PCN catheter segments. Median recoveries after 24-h exposure to pathogens are presented in Fig. 1 for Gram-negative pathogens, Fig. 2 for Gram-positive pathogens, and Fig. 3 for fungal pathogens. At baseline (time zero), M/R-plus-CHD-coated PCN catheter segments completely prevented the formation of biofilm by *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, *Enterobacter* (Fig. 1), methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE) (Fig. 2), *Candida albicans*, and *Candida glabrata* (Fig. 3). The reductions were statistically significant compared to uncoated controls ($P < 0.05$ for all). M/R-plus-CHD PCN catheters also produced significant reductions in colonization relative to M/R PCN catheters for *Enterobacter* spp., *E. coli*, *P. aeruginosa* (Fig. 1), VRE (Fig. 2), *C. glabrata*, and *C. albicans* (Fig. 3) ($P < 0.05$ for all). Control M/R PCN catheters demonstrated reduced colonization versus uncoated PCN catheters against these organisms, but breakthrough colonization was present.

Durability of antimicrobial M/R-plus-CHD PCN catheters. M/R-plus-CHD-coated PCN catheters maintained inhibition against biofilm formation by all challenge pathogens, Gram negative, Gram positive, and *Candida* spp. (Fig. 1 to 3), throughout 3 weeks of incubation.

DISCUSSION

Every obstructed urinary drainage system has the potential to be infected. The results of our study suggest that there may be a significant benefit in using M/R-plus-CHD PCN catheters over an M/R or uncoated PCN catheter for the prevention of biofilm colonization in the catheters. Since catheter colonization is a prelude to infection (15) and M/R-plus-CHD PCN catheters maintained sterile surfaces in the presence of carbapenem-resistant (CRE) *K. pneumoniae*, CRE *E. coli*, MDR *S. maltophilia*, CRE *Enterobacter cloacae*, multidrug-resistant (MDR) *P. aeruginosa*, MRSA, VRE, *C. albicans*, and *C. glabrata* for up to 3 weeks, further testing is warranted to evaluate potential reduction

FIG 1 Antimicrobial efficacy and 3-week durability of M/R-plus-CHD PCN catheters against Gram-negative pathogenic organisms. Inhibition of biofilm colonization by M/R-plus-CHD PCN catheters was tested against CRE *K. pneumoniae* (A), CRE *E. coli* (B), MDR *P. aeruginosa* (C), MDR *S. maltophilia* (D), and CRE *E. cloacae* (E). The durability of the antimicrobial efficacy of M/R-plus-CHD PCN catheters was assessed weekly for up to 3 weeks. All the graphs represent median viable colonies cultured from PCN catheter segments. Uncoated PCN catheters and M/R-impregnated PCN catheters were tested as controls.

of PCN catheter-related UTI or pyelonephritis in a clinical setting. Catheterized patients frequently have abnormal chemistry measurements and elevated protein concentrations in their urine (16). While artificial urine contains only various salts, using serum and plasma in our *in vitro* model allowed us to simulate PCN catheter *in situ* exposure to proteins upon implantation. Based on *in vitro* antimicrobial efficacy, use of M/R-plus-CHD PCN catheters has the potential to prevent infections when the device is inserted into a contaminated system, thus potentially reducing additional complications.

A PCN catheter is an effective method for relieving urinary obstructions caused by various malignancies, allowing the maintenance of renal function. A prospective study conducted by Jalbani et al. showed that PCN catheter placement significantly improved renal function for 75% of patients with malignant ureteral obstruction. Additionally, in the same study, PCN catheter placement and other therapeutic modalities also provided benefits for patients treated for neoplasia (17). The use of PCN catheters has also been shown to increase quality of life at home after urinary diversion procedures are performed (18). However, increased high risk of infection is still a major concern (3). Recent studies have reported rates of PCN catheter-associated pyelonephritis as high as 19% in cancer patients (2). While M/R CVCs have reduced catheter-related bloodstream infections (19), there are no antimicrobial nephrostomy catheters available with the potential to provide prophylaxis for catheter colonization in nephrostomy patients.

FIG 2 Antimicrobial efficacy and 3-week durability of M/R-plus-CHD PCN catheters against Gram-positive pathogenic organisms. Inhibition of biofilm colonization by M/R-plus-CHD PCN catheters was tested against MR *S. aureus* (A) and vancomycin-resistant enterococci (B). The durability of the antimicrobial efficacy of M/R-plus-CHD PCN catheters was assessed weekly for up to 3 weeks. All the graphs represent median viable colonies cultured from PCN catheter segments. Uncoated PCN catheters and M/R-impregnated PCN catheters were tested as controls.

Catheters impregnated with M/R have been previously shown to confer antimicrobial activity in vascular catheters, such as CVCs and peripherally inserted central catheters (PICCs) (8–12). While CHD alone has not been assessed compared to M/R or M/R plus CHD, M/R-plus-CHD CVCs and PICCs have demonstrated superior inhibition of biofilm colonization in previous *in vitro* studies compared with chlorhexidine plus silver sulfadiazine (CHD/SS) and M/R catheters (13, 19). CHD/SS, as assessed in previous studies, is a conservative surrogate, since CHD alone would not have the added benefit of silver sulfadiazine. The addition of a CHD coating to the M/R catheters (M/R plus CHD) not only extended the spectrum of pathogenic protection, but increased the durability of protection for up to 3 weeks (13, 20). The use of the M/R antimicrobial agents has been approved by the FDA for use in CVCs and PICCs. Additionally, CDC guidelines support both the use of antimicrobial CVCs and implementation of bundle precautions for prevention of catheter-related infections (21). Further clinical studies regarding the insertion and maintenance of antimicrobial PCN catheters are needed to translate the technology for use in a nephrostomy setting. In our study, we applied the extended-spectrum (M/R-plus-CHD) coating to nephrostomy catheters and demonstrated broad-spectrum efficacy for up to 3 weeks. According to our data, inhibition of biofilm formation was demonstrated with M/R-plus-CHD PCN catheters against pathogens commonly known to cause PCN catheter-related infections, including multidrug-resistant Gram-positive organisms, Gram-negative organisms, and *Candida* (Fig. 1 to 3).

FIG 3 Antimicrobial efficacy and 3-week durability of M/R-plus-CHD PCN catheters against yeast. Inhibition of biofilm colonization by M/R-plus-CHD PCN catheters was tested against *C. albicans* (A) and *C. glabrata* (B). The durability of the antimicrobial efficacy of M/R-plus-CHD PCN catheters was assessed weekly for up to 3 weeks. All the graphs represent median viable colonies cultured from PCN catheter segments. Uncoated PCN catheters and M/R-impregnated PCN catheters were tested as controls.

In the case of prophylactic antibiotic use during PCN catheter placement, Bahu et al. found the use of prophylactic antibiotics to be unsuccessful in preventing the development of pyelonephritis after PCN catheter placement in cancer patients (2). The same study reported that 48% of pyelonephritis was caused by Gram-positive organisms, 40% by Gram-negative organisms, and 12% by yeast. Our data show significant efficacy and durability of M/R-plus-CHD PCN catheters in the inhibition of biofilm formation for up to 3 weeks against Gram-positive clinical isolates of MRSA and VRE ($P \leq 0.005$), as well as Gram-negative isolates, such as CRE *E. coli*, CRE *K. pneumoniae*, and MDR *P. aeruginosa* ($P \leq 0.05$).

Even when complications are absent, prophylactic exchange of PCN catheters is routinely performed in order to prevent nephrostomy infections (1). These exchange procedures are associated with both economic burdens and morbidities in patients. If PCN catheters are infected, the cost of treatment of acute pyelonephritis is estimated to range from \$605 per episode for outpatient treatment to \$8,500 per episode for inpatient treatment (22). Lagu et al. estimated \$20,000 per episode to treat severe urosepsis (23). In the United States, medical expenses, nonmedical expenses, work loss, and premature death add up to an estimated cost of \$2.14 billion yearly (21). The use of M/R-plus-CHD PCN catheters could potentially increase the life span of PCN catheters, prevent infections, and reduce health care costs in that setting.

While our study demonstrated significant antimicrobial efficacy in a broad spectrum of multidrug-resistant pathogens for 3 weeks, one limitation is that the study was conducted using an *in vitro* model of biofilm colonization. While routine exchange typically occurs every 3 months, patients with PCN catheters are at the highest risk of infection within the first 30 days (2). M/R-plus-CHD PCN catheters demonstrated complete inhibition throughout the duration of testing, with some residual activity extending beyond the highest-risk period. Overall, M/R-plus-CHD PCN catheters proved to be highly efficacious in preventing biofilm colonization when exposed to multidrug-resistant pathogens common to PCN catheter-associated pyelonephritis. Currently, there is no antimicrobial PCN catheter available, and PCN catheters are routinely exchanged in order to prevent infection. As biofilm colonization is the prelude to infection associated with percutaneous catheters, prevention is a key factor in preventing this clinical complication. The use of M/R-plus-CHD PCN catheters requires further clinical assessment. This is necessary to determine if its use can improve patient outcomes and reduce PCN catheter infection and attributable health care economic burdens.

MATERIALS AND METHODS

Microbial strains. A broad spectrum of highly virulent Gram-positive, Gram-negative, and yeast pathogens from our hospital was used for testing. The strains included MRSA (MDA120), VRE (MDA119), MDR *P. aeruginosa* (MDA118), CRE *K. pneumoniae* (MDA125), CRE *E. coli* (MDA123), CRE *E. cloacae* (MDA145), multidrug-resistant *S. maltophilia* (MDA140), *C. glabrata* (MDA115), and *C. albicans* (MDA117). All the pathogens tested were clinical isolates selected from M. D. Anderson Cancer Center (MDA) (Houston, TX) cancer patient cultures. Fresh organism cultures were grown overnight at 37°C on Trypticase soy agar plus 5% sheep blood (for bacteria) or Sabouraud dextrose agar (for yeast) from stored glycerol stocks in our M. D. Anderson Infectious Disease Laboratory's organism library. For testing, pure culture was inoculated into Mueller-Hinton broth (MHB) and diluted to 0.5 McFarland standard. Additional dilutions were made in MHB as necessary for testing.

Antimicrobial efficacy and durability of M/R-plus-CHD nephrostomy tubes. Polyurethane nephrostomy catheters (Cook Medical, Bloomington, IN) were treated with either M/R or M/R plus CHD, utilizing a process similar to one previously used with vascular catheters (13). Briefly, the walls of the nephrostomy catheter were first impregnated with an M/R solution, and following drying, the surfaces were coated with CHD.

Antimicrobial efficacy was tested following the modified Kuhn's biofilm colonization model (24). Briefly, 1-cm segments of M/R, M/R-plus-CHD, and uncoated control catheters were conditioned with donor plasma for 24 h at 37°C. Since urine is the filtrate of whole blood, conditioning was performed in plasma to conservatively simulate exposure of PCN catheters to proteins upon implantation. The plasma was then removed, and the segments were exposed to 1.5×10^5 CFU of microbial inoculum for 24 h at 37°C. The catheters were tested against multidrug-resistant Gram-positive, Gram-negative, and yeast isolates from our institution covering the most significant infectious threats faced by patients with PCN catheters. After 24 h, the microbial inoculum was replaced with 1 ml of 0.9% saline and washed by shaking for 30 min to remove any organisms that were not strongly adherent to the PCN catheters. The

segments were then placed in 5 ml of 0.9% saline and sonicated for 15 min at 40 kHz. After sonication, each control sample was quantitatively cultured, and 100- μ l aliquots were spread onto Trypticase soy agar plus 5% sheep blood (for bacteria) and Sabouraud dextrose agar (for yeast). The plates were incubated inverted for 24 h at 37°C. After incubation, all the plates were counted for viable colonies. All samples were tested in triplicate.

To test the durability of antimicrobial protection, uncoated control, M/R, and M/R-plus-CHD nephrostomy catheters were soaked in serum for up to 3 weeks to simulate biological elution of indwelling drainage catheters. Serum was selected to simulate *in situ* elution of the antimicrobial agents, since catheterized patients frequently have abnormal chemistry measurements and elevated protein concentrations in their urine (16). Catheter segments were removed weekly from the serum and tested for residual antimicrobial activity using the biofilm colonization model described above.

Statistical analysis. Statistical analyses were conducted for comparisons of solutions using a Student *t* test with one-tailed, unequal variances. Since our *a priori* hypothesis predicted that M/R plus CHD would show inhibition superior to that of M/R and the uncoated control, one-tailed tests were conducted. The alpha level was set at 0.05, indicating that a *P* value of <0.05 was significant.

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