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ORIGINAL ARTICLE

# Emergence and prevention measures for multidrug resistant *Pseudomonas aeruginosa* in catheter-associated urinary tract infection in spinal cord injury patients

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**Objective:** To evaluate measures for preventing multidrug resistant *Pseudomonas aeruginosa* (MDRP) in catheter-associated urinary tract infection (CAUTI) in spinal cord injury patients.

**Setting:** Spinal Cord Injury Unit of Hyogo Prefectural Hyogo Prefectural Rehabilitation Center, Kobe, Japan.

**Methods:** We defined MDRP as resistance to amikacin, imipenem and levofloxacin. We had eight cases of MDRP-causing CAUTI in hospitalized neurogenic bladder patients caused by spinal cord injury in 2 months. Pulse-field gel electrophoresis (PFGE) was performed for epidemiological studies. We assessed prevention measures against MDRP emergence from the 2nd month, such as surveillance of CAUTI and infection control, and evaluated the outcomes of these measures over a total of 8 months.

**Results:** Our PFGE results showed that these eight MDRP isolates could be considered as closely related strains. We concluded that this was an MDRP outbreak that was causing CAUTI. The isolated ratio of MDRP began to decrease over 4 months of surveillance and significantly decreased in the 4th quarter (7th and 8th months) compared with the 1st quarter (1st and 2nd months) ($P=0.021$) even though urinary tract device usage significantly increased over the same period ($P<0.001$).

**Conclusion:** We experienced an outbreak of emergent MDRP causing CAUTI in neurogenic bladder patients with spinal cord injury. Our preventive measures for isolating the outbreak, including surveillance, may have led to the decrease we observed in the ratio of MDRP isolated.

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## INTRODUCTION

Catheter-associated urinary tract infection (CAUTI) can have additional complications compared with other urinary tract infection (UTI) due to catheter occlusion and different kinds of causative bacteria. Urinary catheterization is the commonest cause of healthcare facility-acquired infections and complications from CAUTI are a major source of morbidity for spinal injury patients.[1]

UTIs in spinal injury patients have several unique features such as complicated diagnosis due to a lack of symptoms. Another factor in CAUTI is permanent low pressure voiding with permanent indwelling catheters or clean intermittent catheterization.[2] Regarding causative bacteria for CAUTI in spinal injury patients, *Escherichia coli* was the most common isolated pathogen (50%), followed by *Pseudomonas aeruginosa* (17.3%) and *Enterococcus faecalis* (7.7%). Recent antibiotic-resistant strains in UTI include multidrug resistant *P. aeruginosa* (MDRP), which is resistant to aminoglycosides, fluoroquinolones and beta-lactams.[3]

This study reports an outbreak of MDRP in neurogenic bladder CAUTI patients with spinal cord injury. We investigated the epidemiological aspects using pulse-field gel electrophoresis (PFGE), and then assessed our measures for preventing MDRP, including how surveillance affected the MDRP-positive ratio.

## MATERIALS AND METHODS

### Strains

Two MDRP strains were isolated from hospitalized CAUTI patients with neurogenic bladder caused by spinal cord injury and symptomatic UTI at the Department of Urology, Hyogo Prefectural Rehabilitation Hospital (330 beds) in July 2007. Cerebral-vascular diseases and cervical spinal cord injury patients accounted for most hospitalized patients and the average hospital stay was 70.1 days. We then performed surveillance of urine culture tests from all hospitalized patients with catheters or clean intermittent catheterization (number of the urine samples = 171) every month from August 2007 to March 2008.

### Multidrug resistant *Pseudomonas aeruginosa*

MDRP in this study was defined as *P. aeruginosa* resistant to amikacin, imipenem and levofloxacin according to CLSI (Clinical and Laboratory Standards Institute) criteria (Figure 1).[4] The patients with MDRP who had asymptomatic UTI were not given antibiotic treatments to prevent the emergence of antibiotic-resistant strains. However, to evaluate the infection control measures for suppressing MDRP in surveillance, we did not exclude patients with a diagnosis of MDRP over the whole periods of surveillance. Susceptibility testing was performed for sulbactam/ampicillin, cefdinir, cefozopran, flomoxef, isepamicin, imipenem, sulbactam/cefoperazone, sulfamethoxazole/trimethoprim and levofloxacin using Eiken disc plates (Eiken Co. Ltd., Tokyo, Japan) (Figure 1).

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- MDRP

  *P. aeruginosa* resistant to amikacin,imipenem, and levofloxacin (CLSIcriteria: Ref. 4)

- Susceptibility tests (using Eiken disc plates (Eiken Co. Ltd., Tokyo, Japan): CLSI criteria: Ref. 4)

  Antibiotics and concentrations of discs:

  sulbactam/ampicillin: 10/19 μg/mL; cefdinir: 5μg/mL, cefozopran: 30 μg/mL;

  flomoxef: 30 μg/mL; isepamicin: 30 μg/mL; imipenem: 10 μg/mL;

  sulbactam/cefoperazone: 30/75 μg/mL; sulfamethoxazole/trimethoprim:

  23.75/1.25 μg/mL; levofloxacin: 5 μg/mL

**Figure 1** Methods for microbiological evaluation were shown. The definition of MDRP in this study and susceptibility tests were shown.

**Table 1 Surveillance of MDRP**

| | *1st month* | *2nd month* | *3rd month* | *4th month* | *5th month* | *6th month* | *7th month* | *8th month* |
|---|---|---|---|---|---|---|---|---|
| MDRP cases (*n*) | 4 | 4 | 3 | 1 | 2 | 2 | 1 | 1 |
| Total days of catheter use | 460 | 607 | 642 | 705 | 731 | 733 | 866 | 785 |
| Isolated ratio[a] (/1000 devices) | 8.70 | 6.59 | 4.67 | 1.42 | 2.74 | 2.73 | 1.15 | 1.27 |
| Total hospitalized patients | 1289 | 1329 | 1303 | 1334 | 1399 | 1367 | 1495 | 1411 |
| Ratio of catheter use[b] | 0.36 | 0.46 | 0.49 | 0.53 | 0.52 | 0.54 | 0.58 | 0.56 |

Abbreviation: MDRP, multidrug resistant *Pseudomonas aeruginosa*.
[a]Isolated ratio $= \frac{\text{MDRP cases} \times 1000}{\text{Total days of catheter use}}$.
[b]Ratio of catheter use $= \frac{\text{Total days of catheter use}}{\text{Total hospitalized patients}}$.

### Pulse-field gel electrophoresis

The isolates underwent molecular typing by PFGE using the GenePath kit (Bio-Rad, Hercules, CA, USA) and the restriction enzyme *Spe*I. Pairwise comparisons of isolates by PFGE were interpreted on the basis of the criteria reported by Tenover *et al.*[5] Isolates were considered as identical if none of their bands differed, as closely related if one to three of their bands differed and as possibly related if four to six of their bands differed. Isolates differing by more than six bands were assumed to arise from different strains.

### Measures for prevention of MDRP emergence

After the emergence of two MDRP cases, we undertook five measures to prevent MDRP emergence as follows: (1) Urine culture tests for all hospitalized patients with catheters or on clean intermittent catheterization every month. (2) Thoroughness and checking of hand washing before and after medical managements and glove usage every day in the morning conference. (3) Thoroughness and checking of standard precautions and introduction of contact precautions in infected patients once a week in ICT (Infection Control Team) round. (4) Fitting up automatic flushing toilet system. (5) Stop the use of common shelves for personnel antiseptic solution or catheter-preserving liquid. Surveillance under these measures was initiated at the beginning of the 1st month evaluated at the end of the month by urine culture tests. We did not exclude any patients with a diagnosis of MDRP over the whole periods of surveillance because the purpose of this study was to investigate whether the preventive measures were effective for suppressing the emergence and spread of MDRP in surveillance.

The number of MDRPs per 1000 urinary tract devices and urinary tract catheters used per day from total number of hospitalized patients were determined in every month for 8 months. The MDRP isolated ratio was calculated as the number of MDRP cases $\times 1000$ divided by the period of device use (days), and the ratio of urinary tract device use was calculated as the period of device use (days) divided by the number of total hospitalized patients (Table 1).

### Statistical analyses

Statistical analysis was conducted using the chi-square test with Stat View Ver.5.0 (SAS Institute Inc., Cary, NC, USA). Statistical significance was established at the 0.05 level.

## RESULTS

### MDRP strains

The first two MDRP strains isolated from CAUTI patients with neurogenic bladder caused by spinal cord injury were susceptible to cefozopran on July 2007. Our surveillance of all the catheterized patients from August 2007 to March 2008 on one floor, including clean intermittent catheterization patients, found 18 MDRP-positive urine culture tests in 8 patients out of 171 urine samples over the 8 months, and 2 of the 4 strains isolated in the 1st month of surveillance were susceptible to cefozopran. These 171 urine samples for surveillance from 41 patients whose underlying diseases included 38 spinal cord injuries, 1 encephalomyelitis, 1 dissecting aneurysm of the aorta and 1 extradural spinal tumor. One strain was also susceptible to sulbactam/cefoperazon and gentamicin. All cases with MDRP were diagnosed as asymptomatic UTI and were not treated by antibiotics.

### Measures for MDRP outbreak

We took measures for MDRP outbreak shown in a chart (Figure 2). These measures were performed by ICT and detected the possible origin (the common shelf for antiseptic solution storage) of MDRP outbreak and took the appropriate interventions, resulted in the end of this outbreak.

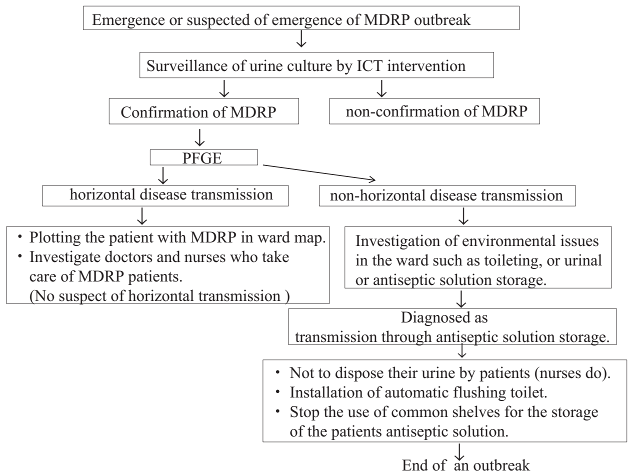


**Figure 2** Flow charts of the intervention from ICT in this MDRP outbreak were shown.

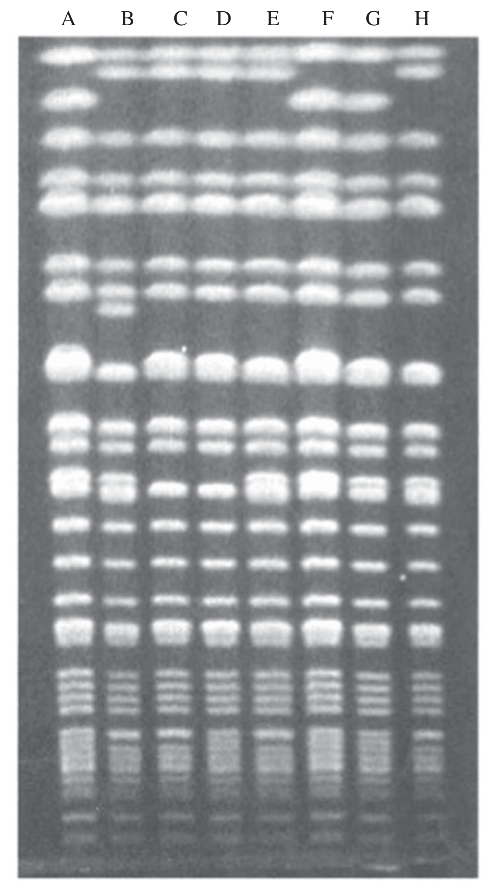


**Figure 3** Band patterns of PFGE of MDRP isolates based on an unweighted-pair group method with average linkages. About 25 bands were fragmented by *Spe*I, and most of these sizes were common. The number of different sized bands was <4, so these eight bands were considered as closely related. These were categorized into five clusters (I: A, F and G; II: B; III: C; IV: D: V: E and H).

### Pulse-field gel electrophoresis

We detected eight cases of MDRP in the first 2 months and performed an urgent PFGE study after the 2nd month because we suspected a horizontal disease transmission of infection in the hospital. The PFGE results for these eight MDRP strains showed that these strains were closely related based on the DNA fragments divided by *Spe*I enzyme (Figure 3). This result suggested that this was an outbreak of MDRP causing CAUTI. These eight MDRP strains were categorized into five clusters by *Spe*I classification.

### Surveillance for MDRP

After initiating the MDRP prevention measures described in Materials and methods, we detected 18 MDRPs in 8 months of surveillance (Table 1). No strains were metallo-beta lactamase producing. Over the surveillance period, the isolation ratio of MDRP began to decrease in the first 4 months and significantly decreased in the 4th quarter (7th and 8th months) compared with the 1st quarter (1st and 2nd months) ($P=0.021$) even though urinary tract device use significantly increased during the same time period ($P<0.001$) (Figure 4). Our measures to prevent MDRP emergence shown in Materials and methods section cost 1580 USD over the whole surveillance period, and the breakdown is that 920 USD for bacterial tests and antibiotic susceptibility examinations and 660 USD for installation of automatic flushing toilet for disposing of urine or waste without touching a lever (Figure 5).

## DISCUSSION

Bilavsky *et al.*[6] recently described three cases of MDRP in UTI after urodynamic studies and identified a urodynamic pressure transducer as the source of this outbreak, which was verified by PFGE. These strains showed susceptibility only to colistin. Other authors reported a urodynamic study-related *P. aeruginosa* outbreak and discussed the propriety of reusing single-use medical devices for cost reduction.[7] Bilavsky *et al.*[6] suggested that not reusing urodynamic pressure transducers, as an infection control measure, could avoid similar MDRP outbreaks. Our study of the emergence and subsequent prevention of MDRP in neurogenic bladder CAUTI patients with spinal cord injury is meaningful in the context of device-related hospital infections.

Our eight cases in the initial 2 months of our survey of CAUTI in neurogenic bladder patients with spinal cord injury had no apparent detectable relationship, but the infection control measures we initiated, including reinforcement of glove use, standard precautions and contact precautions and hand washing, had some effect from the 3rd month and decreased the ratio of MDRP occurrence. It is possible that transmission by medical staff dealing with catheters might be one possible cause of MDRP outbreaks. Seki *et al.*, in their report of an MDRP outbreak, suggested several possible causes for the outbreak including a contaminated device or environmental contamination that could be responsible for transmission of the pathogen.[8,9] Our initial eight MDRP cases were all from the same wards (4th floor, East) and it is possible that catheter devices or the hands or gloves of medical staff in the same ward might have caused this outbreak.

Risk factors for MDRP outbreak or *P. aeruginosa* infection include the presence of indwelling devices, admission to an intensive care unit, prior antibiotic use, length of hospitalization, severe underlying disease and impaired immunity.[10,11] Mudau *et al.*[12] reported that in their outbreak of nine cases of MDRP blood stream infection in patients with hematological conditions, the risk factors for MDRP blood stream infection included acute myelogenous leukemia, and that previous use of amikacin and metronidazole was independent risk factors based on their multivariate analyses. Our cases had no

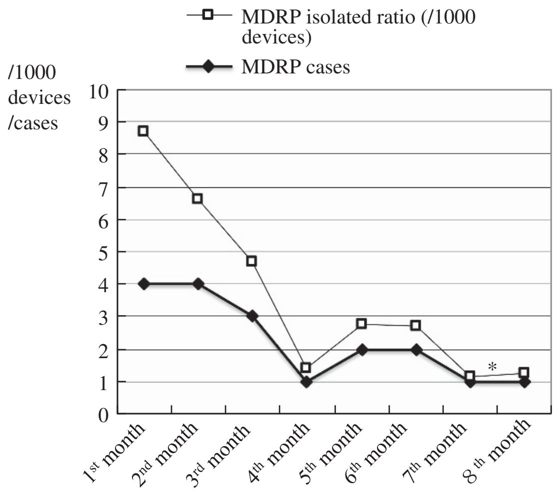


**Figure 4** Changes in MDRP isolated ratio and isolated cases over all observed surveillance periods. The MDRP isolated ratio was calculated by the formula: MDRP cases × 1000/Total days of catheter use (Table 1). The asterisk (*) shows where the isolated ratio significantly decreased in the 4th quarter (7th and 8th months) compared with the 1st quarter (1st and 2nd months) ($P = 0.021$).

available data on previous antibiotic use but this factor needs to be investigated in future studies. However, all of our cases were neurogenic bladder patients caused by spinal cord injury or cerebrovascular disease and such patients may be considered as immune-compromised hosts because of poor performance status.

Debate continues whether bacterial isolation in CAUTI constitutes infection and colonization for decision-making purposes or requires a therapeutic strategy.[13] However, our CAUTI included patients with disturbances of consciousness, who may need different standards of care, and any colonization or contamination has potential risks for outbreak. Therefore, considering our patients' backgrounds, we included colonized UTI in our evaluation.

There is also debate about the definition of MDRP. Some authors define this as *P. aeruginosa* resistant to ceftazidime, ciprofloxacin, piperacillin, imipenem and amikacin,[4,14,15] but this definition has not been agreed on internationally. Some of our MDRPs showed susceptibility to several antibiotics, for instance cefozopran.

Regarding the best measures for preventing MDRP, including active surveillance or infection control, Saurez *et al.*[16] included rectal swabs in an ICU unit over a 1-month period and weekly rectal swab samples obtained on admission among their methods. As to infection control, disposable aprons and gloves were used when dealing with materials and instruments for MDRP-colonized/infected patients, and cleaning procedures were strictly checked by infection control nurses. These precautions were also undertaken by our hospital. Next, environmental cleaning was reinforced.

Regarding the cost-effectiveness, even though the direct comparison may be hard, the patient with drug-resistant *P. aeruginosa* required higher costs than drug-susceptible *P. aeruginosa* (81330 USD vs 48381USD in meropenem resistance[17] and 62325 USD vs 48734 USD in fluoroquinolone resistance),[18] our results showed MDRP cases decreased in the last half over the whole periods of surveillance (12 patients in the first 4 months vs 6 patients in the last 4 months). Taken together, our measures for prevention of MDRP (1580 USD) might be considered as good cost-effectiveness.

We would like to emphasize the study limitations. Data on previous antibiotic use were not available and this may be relevant to MDRP occurrence. Next, information on the patients' backgrounds was not complete. These data are necessary for evaluation of the risk factors for MDRP outbreak. Third, the MDRP urine samples included samples from the same patients in 8-month surveys. This is because our study is retrospective and had consecutive patient cases without any exclusions to examine the real clinical setting, and for that we adjusted our statistics by isolated MDRP ratio and ratio of catheter use. These limitations will be overcome in our future studies.

**Figure 5** A picture of automatic flushing toilet for disposing of urine or waste without touching a lever.

## CONCLUSION

We reported an emergent outbreak of MDRP causing CAUTI in neurogenic bladder spinal cord injury patients. Our measures for isolating and preventing the spread of this outbreak included surveillance and infection control and may have led to a decrease in the isolated MDRP ratio even though the direct correlation is hard to trace. Further investigations will address the prevention of outbreaks not only of MDRP but also of other kinds of resistant strains as well.

## DATA ARCHIVING

There were no data to deposit.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.


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