*Infection Control & Hospital Epidemiology* (2019), **40**, 217–220
doi:10.1017/ice.2018.331

## Concise Communication

# A metallo-beta-lactamase producing Enterobacteriaceae outbreak from a contaminated tea dispenser at a children's hospital in Japan

Kenta Ito MD[1], Hitoshi Honda MD, PhD[2], Makiko Yoshida PhD, MPH[3], Kotaro Aoki PhD[4], Yoshikazu Ishii PhD[4], Shigeko Miyokawa[5] and Yuho Horikoshi MD[1]

[1]Division of Infectious Diseases, Department of Pediatrics, Tokyo Metropolitan Children's Medical Center, Fuchu, Tokyo, Japan, [2]Division of Infectious Diseases, Department of Medicine, Tokyo Metropolitan Tama Medical Center, Fuchu, Tokyo, Japan, [3]Department of Infection Control and Laboratory Diagnostics, Tohoku University Graduate School of Medicine, Sendai, Japan, [4]Department of Microbiology and Infectious Diseases, Toho University School of Medicine, Tokyo, Japan and [5]Department of Nursing, Tokyo Metropolitan Children's Medical Center, Fuchu, Tokyo, Japan. (Present affiliation: Department of General Pediatrics, Aichi Children's Health and Medical Center, Ohbu, Aichi, Japan [K.I.].)

**Abstract**

An outbreak of metallo-β-lactamase (MBL) producing *Klebsiella pneumoniae* occurred at a children's hospital in Japan. MBL-producing *K. pneumoniae* was detected in tea dispenser in the hospital, the use of which was associated with the acquisition of the MBL-producing Enterobacteriaceae. The outbreak ceased after use of the tea dispenser was banned.

(Received 4 September 2018; accepted 13 November 2018)

The emergence of carbapenemase-producing Enterobacteriaceae (CPE) is a public health threat requiring global action.[1] Although CPE is still considered rare and constitutes < 1% of the Enterobacteriaceae isolated in Japan,[2] the clinical impact of CPE infections on morbidity and mortality are substantial; the mortality rate due to CPE sepsis among adult patients in Japan was reportedly as high as 40%.[3]

Healthcare-related outbreaks of metallo-β-lactamase (MBL)-producing Enterobacteriaceae have been reported in various settings including pediatric wards and pediatric intensive care units.[4] We experienced an outbreak of MBL-producing Enterobacteriaceae lasting from May to December 2014 in a pediatric ward at Tokyo Metropolitan Children's Medical Center. We report the subsequent outbreak investigation and the infection control measures implemented.

## Methods

The MBL-producing Enterobacteriaceae outbreak occurred at a single, pediatric, joint cardiology and ophthalmology ward with 27 beds. Apart from this outbreak, a patient colonized by MBL-producing Enterobacteriaceae had been hospitalized in isolation in the same ward for a prolonged period. In May 2014, MBL-producing *Klebsiella pneumoniae* was discovered incidentally while testing for *Clostridium difficile* in a stool culture of a patient with chronic diarrhea. The results of the test were negative for *Clostridioides difficile*. Shortly thereafter, MBL-producing Enterobacteriaceae were detected in 2 more patients in the same ward. Immediate active surveillance for the pathogen was implemented. Initial active surveillance by rectal swab identified 6 more patients colonized by the same pathogen. The unusually high occurrence of this strain confirmed an MBL-producing Enterobacteriaceae outbreak in the ward. The Ethics Committee of Tokyo Metropolitan Children's Medical Center approved the study protocol (No. H26-108)

Weekly active surveillance to detect MBL-producing Enterobacteriaceae was conducted for all patients in the ward without a previous history of colonization or infection due to MBL-producing Enterobacteriaceae.[5] Rectal swab cultures were obtained from hospitalized patients once weekly.

Rectal swabs were inoculated onto a cefpodoxime-containing agar (ChromID ESBL SYSMEX, bioMerieux, Japan). The resulting blue or purple colonies were planted onto blood agar with a cefoxitin disc and boronic acid to inhibit the isolates from overproducing AmpC β-lactamase. The sodium mercaptoacetate (SMA) test (Eiken Chemical, Japan) was performed on these isolates to detect MBL-producing Enterobacteriaceae. Two discs containing ceftazidime with or without SMA were placed on Mueller-Hinton agar 4–5 cm apart. The bacterial strain was diluted by saline to the 0.5 McFarland standard and placed on Mueller-Hinton agar. A difference > 5 mm in the growth inhibitory zone was considered evidence of the MBL-producing strain.[6]

We conducted the molecular biological analysis of the isolated MBL-producing Enterobacteriaceae (see Supplemental Materials online). To investigate possible contaminants in the immediate

**Author for correspondence:** Kenta Ito MD, 2-8-29 Musashi-dai Fuchu-shi, Tokyo, Japan. E-mail: peaceplease1981@gmail.com Or Yuho Horikoshi MD, 2-8-29 Musashi-dai Fuchu-shi, Tokyo, Japan. E-mail: yuho_horikoshi@tmhp.jp

PREVIOUS PRESENTATION: These data were presented at IDWeek 2015, October 8, 2015, in San Diego, California, as the winning entry in the International Investigator Awards.

**Cite this article:** Ito K, *et al.* (2019). A metallo-beta-lactamase producing Enterobacteriaceae outbreak from a contaminated tea dispenser at a children's hospital in Japan. *Infection Control & Hospital Epidemiology* 2019, 40, 217–220. doi: 10.1017/ice.2018.331

**Table 1.** Characteristics of Patients who Received an Active Surveillance Culture

| Variable[a] | MBL-Producing Enterobacteriaceae-Positive Patients (n = 36), No. (%)[b] | MBL-Producing Enterobacteriaceae-Negative Patients (n = 109) , No. (%)[b] | *P* Value | Adjusted Odds Ratio (95% CI)[c] |
|---|---|---|---|---|
| Male gender | 23 (63.9) | 51 (46.8) | .08 | |
| Age at admission, median mo (range) | 1 (0–20) | 2 (0–37) | .18 | |
| Underlying diseases | 32 (88.9) | 85 (78.0) | .15 | |
| Use of tea dispenser | 31 (86.1) | 41 (37.6) | .00 | 43.69 (7.33–260.49) |
| History of oral meal intake | 32 (88.9) | 49 (45.0) | .00 | |
| History of tube feeding | 12 (33.3) | 26 (23.9) | 26 | |
| History of maternal feeding | 3 (8.3) | 14 (12.8) | .47 | |
| History of receiving formula | 15 (41.5) | 46 (42.2) | .96 | |
| History of parental nutrition | 2 (5.6) | 1 (0.9) | .15 | |
| History of feeding assistance by nurses | 21 (58.3) | 19 (17.4) | .00 | |
| Processing and preparation of tube-feeding formula in the outbreak ward | 4 (11.1) | 2 (1.8) | .03 | |
| Use of baby bottle | 12 (33.3) | 38 (34.9) | .87 | |
| Use of diapers | 26 (72.2) | 72 (66.7) | .54 | |
| Use of bathroom | 6 (16.7) | 20 (18.3) | .82 | |
| Use of bed bath | 25 (69.4) | 52 (47.7) | .02 | NS |
| History of receiving physiotherapy | 5 (13.9) | 8 (7.3) | .23 | |
| No. of surveillance cultures conducted, median (range) | 1 (1–12) | 1(1–24) | .33 | |
| Duration of admission, median d (range) | 15 (1–284) | 6 (1–196) | .00 | 1.02 (1.01–1.04) |
| History of hospitalization 1 mo prior to the last active surveillance culture | 5 (13.9) | 8 (7.3) | .23 | |
| Previous history of hospital stay at the outbreak ward | 14 (38.9) | 31 (28.4) | .24 | |
| **Primary department** | | | .05 | |
| Cardiovascular internal medicine | 20 (55.6) | 59 (54.1) | | |
| Cardiovascular surgery | 13 (36.1) | 19 (17.4) | | |
| Ophthalmology | 2 (5.6) | 26 (23.9) | | |
| Other | 1 (2.8) | 5 (4.6) | | |
| History of surgery | 13 (36.1) | 27 (24.8) | .19 | |
| History of a cardiac catheterization | 4 (11.1) | 23 (21.1) | .18 | |
| History of echocardiogram | 30 (83.3) | 66 (60.6) | .01 | |
| History of radiography | 33 (91.7) | 86 (78.9) | .08 | |
| Use of central venous catheter | 17 (47.2) | 29 (26.6) | .02 | |
| Use of mechanical ventilation | 17 (47.2) | 30 (27.5) | .03 | |
| Use of urinary catheter | 18 (50.0) | 27 (24.8) | .01 | |
| Use of peripheral venous catheter | 29 (80.6) | 67 (61.5) | .04 | NS |
| Use of antacids | 19 (52.8) | 37 (33.9) | .04 | NS |
| Use of antimicrobials | 24 (66.7) | 58 (53.2) | .16 | NS |

Note. MBL, metallo-β-lactamase; NS, not significant.
[a]Duration of exposure in all of the above categories was within 1 mo prior to obtaining a positive culture for positive patients and the last culture done for negative patients.
[b]No. (%) unless otherwise specified.
[c]By multivariate analysis. Multivariate analysis included use of the tea dispenser, bed bath, antacids, and antimicrobials, and duration of admission in days.

https://doi.org/10.1017/ice.2018.331 Published online by Cambridge University Press

environment, environmental cultures were conducted eight times during the outbreak period from May to December 2014. In total, 195 samples were collected on eight different sampling days (see supplementary materials). A retrospective study was conducted to explore the risk factors of MBL-producing Enterobacteriaceae acquisition. We obtained demographic and clinical data of patients with an active surveillance culture (see Supplementary Materials online).

### Statistical analysis

Univariate analysis was performed using the $\chi^2$ test and the Fisher exact test. The Mann-Whitney *U* test was used for continuous variables. Candidate variables with $P < .10$ in univariate analysis were included in the multivariate analysis. Sensitivity analysis controlling for other covariates was conducted. All statistical analyses were conducted with SPSS version 22 software (IBM, Armonk, NY).

## Results

In total, 249 patients were admitted to the ward during the study period. Active surveillance was performed once weekly except at the time of admission; however, 104 patients did not undergo a rectal swab for the surveillance culture due to their shorter period of hospitalization. The 145 patients who had undergone a rectal swab were included for analysis. The characteristics of these patients are shown in Table 1.

Overall, 36 patients (24.8 %) yielded a total of 39 strains of MBL-producing Enterobacteriaceae including 30 cases of *K. pneumoniae*, 5 cases of *Escherichia coli*, 2 cases of *Citrobacter freundii*, 1 case of *Klebsiella oxytoca*, and 1 case of *Enterobacter aerogenes*.

MBL-producing *K. pneumoniae* was isolated from 7 environmental samples (3.6 %). At the first sampling, a sink in the nurses' station tested positive. At the third sampling, another sink in the nurse's station and the milk bottle cabinet were positive. Finally, at the eighth sampling, 4 positive samples were obtained from the tea dispenser.

We sequenced the whole genome of 37 *K. pneumoniae* strains isolated from the clinical and environmental samples. All isolates harbored the $bla_{\text{IMP-1}}$ gene. A core-genome single nucleotide polymorphism (SNP)–based phylogenetic analysis revealed that 33 of the $bla_{\text{IMP-1}}$-positive *K. pneumoniae* strains had a common ancestor (see the Supplementary Materials online).

### Risk factor analysis

The results of our univariate analysis exploring the risk factors of MBL-producing Enterobacteriaceae acquisition are shown in Table 1. Our multivariate analysis revealed that use of the tea dispenser (adjusted OR [aOR], 43.69; 95% CI, 7.33–260.49) and longer length of hospital stay (aOR, 1.03; 95% CI, 1.01–1.04) were associated with the acquisition of these pathogens. Sensitivity analysis controlling for other covariates did not affect the results of the multivariate analysis.

### Infection control measures

We applied strict cohorting of patients with MBL-producing Enterobacteriaceae. Use of public areas such as the playroom and dining hall in the ward was banned due to the potential sources of transmission. Staff education in appropriate standard and contact precautions was reinforced. Routine environmental cleaning, including cleaning of the sinks and frequently touched areas using 0.1 % hypochlorite was increased from 1 to 3 times daily. Admission to the ward was restricted twice during the outbreak to prevent spreading the pathogens. No MBL-producing Enterobacteriaceae were isolated from patients admitted to the ward or occupying the ward environment after banning the use of the tea dispenser.

## Discussion

We have described the largest documented pediatric outbreak of $bla_{\text{IMP-1}}$-positive *K. pneumoniae* in Japan. Environmental sampling and epidemiological investigation identified a tea dispenser in the ward as the contaminant source.

The tea dispenser, placed in a public area in the ward for the use of patients and visitors, automatically mixes barley tea powder with hot water in a shaker before diluting with cold water and dispensing the liquid as iced tea. The maintenance and cleaning of the tea dispenser were done by the cleaning staff using detergents once daily according to the manufacturer's instructions. The cleaning staff were also responsible for the disposal of the children's diapers in the ward. MBL-producing Enterobacteriaceae were detected in the shaker, which was handled only by the cleaning staff, suggesting that it had become contaminated by their handling. An interview of the cleaning staff later revealed that their knowledge and practice of hand hygiene were inadequate. Self-service tea and water dispensers, commonly available to patients in medical facilities throughout Japan, may readily act as a medium for infection among a patient population if contaminated.

However, reports of CPE outbreaks among the pediatric population are rare, and the mode of transmission has never been clarified.[7,8] Moreover, existing reports have focused on the molecular characteristics of CPE or were unable to determine the route of transmission due to inadequate outbreak investigation. In contrast, in our study, rigorous outbreak investigation and comprehensive molecular typing demonstrated that a tea dispenser was the likely source of transmission. The surveillance cultures of the environmental samples in the present study revealed that 2 cultures from the sinks in the nurses' station were positive for MBL-producing *K. pneumoniae*. It is likely that these positive results are due to environmental contamination because the outbreak continued despite rigorous cleaning of these areas. Another hypothesis proposes that water supplied in the hospital was contaminated by MBL-producing *K. pneumoniae*, but this is unlikely because none of the clinical samples from other wards yielded the pathogens, and cultures of the water samples from the tea dispenser were also negative.

The phylogenetic analysis based on core-genome SNPs revealed that the $bla_{\text{IMP-1}}$-positive ST34 *K. pneumoniae* isolated in the outbreak had a common ancestor (see Supplementary Materials online). Therefore, the analysis suggested that the tea dispenser was the source.

Also, a longer stay in the ward was significantly related to CPE colonization. Usually, a long hospital stay is a risk factor for acquiring CPE,[9] but its relationship to CPE acquisition is weaker than in the present case of the use of the tea dispenser. We assume that the longer hospital stay created more opportunities for using the contaminated tea dispenser.

In summary, we experienced an outbreak of IMP-1 MBL-producing Enterobacteriaceae among pediatric patients in a tertiary-care children's hospital. After rigorous investigation, a cold tea dispenser was identified as the source of contamination. Despite the rarity of this mode of transmission, infection control

https://doi.org/10.1017/ice.2018.331 Published online by Cambridge University Press

personnel should be aware of its possibility whenever a MBL-producing Enterobacteriaceae outbreak occurs.

**Supplementary materials.** To view supplementary material for this article, please visit https://doi.org/10.1017/ice.2018.331

**Acknowledgments.** We thank Dr Isao Miyairi, Mie Sugawara, Dr Ken Hori, Dr Naoya Fukushima, and Dr Masaru Miura for their cooperation and advice in our outbreak investigation and James R. Valera for his assistance in editing the manuscript.

**Financial support.** No financial support was provided relevant to this article.

**Conflicts of interest.** All authors report no conflicts of interest relevant to this article.

## References

1. Magiorakos AP, Suetens C, Monnet DL, Gagliotti C, Heuer OE. The rise of carbapenem resistance in Europe: just the tip of the iceberg? *Antimicrob Resist Infect Control* 2013;2:6.
2. Suzuki S, Matsui M, Suzuki M, Tsutsui A, Shibayama K. The surveillance report of carbapenem-resistant enterobacteriaeceae infection based on infectious disease law in Japan, 2014. http://www0.nih.go.jp/niid/idsc/iasr/35/418j.pdf. Published 2014. Accessed January 26, 2015.
3. Hayakawa K, Miyoshi-Akiyama T, Kirikae T, *et al*. Molecular and epidemiological characterization of IMP-type metallo-beta-lactamase-producing *Enterobacter cloacae* in a large tertiary care hospital in Japan. *Antimicrob Agents Chemother* 2014;58:3441–3450.
4. Stillwell T, Green M, Barbadora K, *et al*. Outbreak of KPC-3 producing carbapenem-resistant *Klebsiella pneumoniae* in a US pediatric hospital. *J Pediatr Infect Dis Soc* 2015;4:330–338.
5. Laboratory protocol for detection of carbapenem-resistant or carbapenemase-producing, *Klebsiella* spp. and *E. coli* from Rectal Swabs, 2012. Centers for Disease Control and Prevention website. http://www.cdc.gov/hai/pdfs/labSettings/Klebsiella_or_Ecoli.pdf. Published 2012. Accessed May 7, 2015.
6. Arakawa Y, Shibata N, Shibayama K, *et al*. Convenient test for screening metallo-beta-lactamase-producing gram-negative bacteria by using thiol compounds. *J Clin Microbiol* 2000;38:40–43.
7. Liu Y, Li XY, Wan LG, Jiang WY, Li FQ, Yang JH. Molecular characterization of the bla(KPC-2) gene in clinical isolates of carbapenem-resistant *Klebsiella pneumoniae* from the pediatric wards of a Chinese hospital. *Can J Microbiol* 2012;58:1167–1173.
8. Benenson S, Warburg G, Hidalgo-Grass C, *et al*. Comparison of two carbapenem-resistant Klebsiella pneumoniae clones: from a contained outbreak in a paediatric population and from a national epidemic. *J Antimicrob Chemother* 2012;67:1651–1654.
9. Montagnani C, Prato M, Scolfaro C, *et al*. Carbapenem-resistant Enterobacteriaceae infections in children: an Italian retrospective multicenter study. *Pediatr Infect Dis J* 2016;35:862–868.