The burden of *Clostridiodes difficile* infection in Japan: a prospective multi-center study

Haru Kato,¹ Mitsutoshi Senoh,¹ Hitoshi Honda,² Yasuaki Tagashira,² Erik R. Dubberke,³ Kimberly Reske,¹ Margaret A. Olsen¹ and The *Clostridiodes difficile* infection Japan Study Group

¹National Institute of Infectious Diseases, Tokyo, Japan; ²Tokyo Metropolitan Tama Medical Center, Tokyo, Japan; ³Washington University School of Medicine, St. Louis, Missouri, USA

**Background:**
Despite predisposing factors for *Clostridiodes* (*Clostridium*) difficile infection (CDI) such as increasing age in Japan, retrospective studies have generally found a lower incidence than those reported from Europe and North America. There are several potential explanations, including testing practices and strain distribution.

We conducted a multicenter study at 12 medical facilities to determine CDI incidence and molecular epidemiology in Japan.

**Study design:**
1. From May 12, 2014 to May 11, 2015, all patients 18 years of age or older with clinical significant diarrhea (CSD) were approached to participate in the study.
2. CSD was defined as follows: at least 3 diarrheal bowel movement (Bristol stool chart grade 6-7) in the prior 24 hours, or a diarrheal bowel movement (Bristol stool chart grade 6-7) associated with abdominal cramping.
3. CDI was defined as CSD with any of positive results of *C. difficile* toxin A/B by enzyme immunoassay (EIA), toxigenic culture (TC) and nucleic acid amplification test (NAAT).

**Laboratory assays and C. difficile analysis**
1. Detection of fecal toxin by EIA was performed at each hospital.
2. Stool specimens were cultured on CCMA-EX (Nissui) after treating with alcohol for spore selection. CCMB-TAL (Anaerobe Systems) was also used. The presence of genes encoding toxin A, toxin B and binary toxin (CDT) was examined by PCR.
3. NAAT was performed by detection of the toxin B gene from fecal specimens by BD MAX Cdiff Assay kit (BD Diagnostics).
4. Typing analysis was performed by PCR-ribotyping (RT) and spa.4 sequence typing (spa.4-ST).
5. Susceptibility testing was carried out by using Etest strips (bioMérieux SA).

**Table 1. Comparison of CDI incidence rate by ward type**

<table>
<thead>
<tr>
<th>Ward (No. of wards examined)</th>
<th>No. of CDI cases</th>
<th>CDI incidence rate per 10,000 pd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical (n=10)</td>
<td>86</td>
<td>6.0</td>
</tr>
<tr>
<td>ICU (n=4)</td>
<td>45</td>
<td>22.2</td>
</tr>
<tr>
<td>Medical/surgical (n=3)</td>
<td>13</td>
<td>3.2</td>
</tr>
<tr>
<td>Surgical (n=2)</td>
<td>29</td>
<td>9.0</td>
</tr>
<tr>
<td>All (n=20)</td>
<td>173</td>
<td>7.4</td>
</tr>
</tbody>
</table>

The high incidence in 5 ICU wards indicates that intervention designed to reduce CDI in ICUs may be particularly critical.

**Conclusions:**
1. A sizable number of patients with CDI are not identified due to low testing rates in Japan.
2. It is suggested that selective pressure by overuse of antimicrobial agents leads to the spread of *C. difficile*, especially of RT 018/018*°* and RT369.
3. It is important to raise the awareness of infection control for CDI, including optimal laboratory diagnosis and implementation of antimicrobial stewardship programs in Japan.

**Table 2. Correlation of CDI testing rate and CDI incidence rate**

**Figure:** Typing results by PCR-ribotyping

**Table 3. Typing results of recovered isolates and CDI incidence per ward**

**Table 4. Susceptibility of 146 isolates against 8 antimicrobial agents**

**The Clotridiodes difficile infection Japan Study Group**

Hachinohe City Hospital, Kameda Medical Center, NHO Tokyo Medical Center, Tokyo Bay Urayasu Ichikawa Medical Center, Toyosawa City Hospital, Tokai Central Hospital, Nara Medical University, NHO Toneyama National Hospital, University Hospital, University of Occupational and Environmental Health, NHO Kure Medical Center, Shimonsoki City Hospital, Okinawa Prefectural Nanbu Medical Center and Children’s Medical Center

*Correspondence Haru Kato (cato@nih.go.jp)

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