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Original Article

Perceptions of *Clostridium difficile* infections among infection control professionals in Taiwan

Yuan-Pin Hung [a,c,e], Jen-Chieh Lee [c], Hsiao-Ju Lin [a,c,e], Chun-Wei Chiu [a,c,e], Jia-Ling Wu [c], Hsiao-Chieh Liu [a,b], I-Hsiu Huang [h], Pei-Jane Tsai [g,h,i], Wen-Chien Ko [c,d,f,*]

[a] *Department of Internal Medicine, Tainan Hospital, Ministry of Health & Welfare, Tainan, Taiwan*
[b] *Department of Experiment and Diagnosis, Tainan Hospital, Ministry of Health & Welfare, Tainan, Taiwan*
[c] *Department of Internal Medicine, National Cheng Kung University Hospital, Tainan, Taiwan*
[d] *Center of Infection Control, National Cheng Kung University Hospital, Tainan, Taiwan*
[e] *Graduate Institute of Clinical Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan*
[f] *Department of Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan*
[g] *Department of Medical Laboratory Science and Biotechnology, College of Medicine, National Cheng Kung University, Tainan, Taiwan*
[h] *Department of Microbiology and Immunology, College of Medicine, National Cheng Kung University, Tainan, Taiwan*
[i] *Center of Infectious Disease and Signaling Research, National Cheng Kung University, Tainan, Taiwan*

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Abstract *Background:* High *Clostridium difficile* colonization and infection rates among hospitalized patients had been noted in Taiwan. Nevertheless, the cognition about clinical diagnosis and management of CDI among infection control professionals in Taiwan is not clear.
Material and methods: A 24-item survey questionnaire about the diagnosis, therapy, or infection control policies toward CDI was distributed in the annual meeting of the Infectious Disease Society of Taiwan (IDST) in October 2015 and Infectious Control Society of Taiwan (ICST) in April 2016.
Results: Totally 441 individuals responded to the survey, and 280 (63.5%) participants would routinely monitor the prevalence of CDI and 347 (78.7%) reported the formulation of infection control policies of CDI in their hospital, including contact precaution (75.7%), wearing gloves (88.9%) or dressing (80.0%) at patient care, single room isolation (49.7%), preference of soap or disinfectant-based sanitizer (83.2%) and avoidance of alcohol-based sanitizer (63.3%), and

* Corresponding author. Department of Internal Medicine, National Cheng Kung University Hospital, No. 138, Sheng Li Road, Tainan, 70403, Taiwan. Fax: +886 6 2752038.
E-mail address: winston3415@gmail.com (W.-C. Ko).

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environmental disinfection with 1000 ppm bleach (87.1%). For the timing of contact precaution discontinuation isolation for CDI patients, most (39.9%) participants suggested the time point of the absence of *C. difficile* toxin in feces. To treat mild CDI, most (61.9%) participants preferred oral metronidazole, and for severe CDI 26.1% would prescribe oral vancomycin as the drug of choice.

Conclusion: There were substantial gaps in infection control polices and therapeutic choices for CDI between international guidelines and the perceptions of medical professionals in Taiwan. Professional education program and the setup of guideline for CDI should be considered in Taiwan.

Introduction

Clostridium difficile is the major infectious cause of antibiotic-associated diarrhea. The clinical presentation of *C. difficile* infection may range from mild diarrhea to pseudomembranous colitis and toxic megacolon.[1] Patients developing CDI was associated with higher mortality: the attributable cause of death in 7% of cases and a contributing factor in additional 7.5% of cases during an outbreak[2] and higher health care costs: annual attributable costs exceed $1.5 billion in the United States.[3] High *C. difficile* colonization and infection rates were also noted in Taiwan.[4–6] The notorious effect of *C. difficile* could be attributed to the appearance of hypervirulent strain, such as the North American pulse-field type 1 (NAP1), restriction endonuclease analysis (REA) group BI, and polymerase chain reaction (PCR) ribotyping 027 (referred to as BI/NAP1/027) which is characterized as: increased production of toxin A and B, fluoroquinolone resistance, and production of binary toxin.[1]

CDI is an important infection control issue because *C. difficile* is frequently transmitted in healthcare settings via health care workers[7] and spores of *C. difficile* which are resistant to alcohol and common detergents are shed by the patients with *C. difficile* colonization or infection.[8] According to the clinical guidelines for *C. difficile* infection in adults: 2010 update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) and the update of the treatment guidance document for CDI on 2014 of European Society of Clinical Microbiology and Infectious Diseases (ESCMID), some suggestions in diagnosis, treatment, and infection control policies had been proposed, such as only CDI testing in symptomatic patients, no test of cure after CDI treatment, vancomycin as preferred treatment for severe or complicated disease.[9,10]

In Taiwan, the first hypervirulent *C. difficile* clone, ribotype 126, causing pseudomembranous colitis and recurrent CDAD was reported on 2014[11] and the first patient infected by a ribotype 027 isolate causing pseudomembranous colitis and toxic megacolon on 2015.[12] Furthermore a high *C. difficile* colonization and infection rate was noted,[13] suggestive of the potential health threat in this island. Nevertheless, here not clear are the perceptions of international consensus of therapeutic choices and infection control measures of CDI among infection control professionals, which is our study purpose.

Materials and methods

A 24-item questionnaire with three domains, including diagnostic modalities, antimicrobial therapy, and infection control interventions, was formulated (Table 1). These items were derived from clinical practice guidelines for *C. difficile* infection issued by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA)[9] and were revised by infection control professionals, including four infectious disease specialists and four experienced infection control nurses. Demographic data, working position and experience of the members of the Infectious Disease Society of Taiwan (IDST) and the Infectious Control Society of Taiwan (ICST), two major professional societies of infectious diseases and infection controls in Taiwan, and their responses to the above questionnaire were collected anonymously at annual meetings in March 2016. The study was approved by the institutional review board of National Cheng Kung University Hospital (IRB number: B-EX-104-021).

Statistical analysis was performed by the statistical software (SPSS, version 20.0). Continuous data were expressed as the means ± standard deviations. The χ^2 test or Fisher's test was used for categorical variables, and the Student *t*-test for continuous variables. A two-tailed *P* value of less than 0.05 was considered to be statistically significant. The parameters with *P* values less than 0.05 in the univariate analysis were entered into a multivariate analysis with a binary logistic regression model. The Bonferroni correction for multiple testing was applied. For internal consistency reliability, the Cronbach's coefficient alpha of the study was measured by SAS, version 9.4 (SAS Institute, Cary, NC).

Results

A total of 441 individuals responded to the questionnaires with 176 (39.9%) were males. Their work places included medical centers (103, 23.1%), district hospitals (114, 25.9%), local hospitals (103, 23.4%), clinics (30, 6.8%) and others (91, 20.6%), as shown in Table 2. The Cronbach's

Table 1 The items of the questionnaire of *Clostridium difficile* infection (CDI) and related recommendations from the guidelines of the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA), 2010.

Recommendations	Strength of recommendations and quality of evidence
Infection control measures	
Routine monitor patients with CDI	B—III
Wear gloves at care	A—I
Wear gowns at care	B—III
Single room isolation	C—III
Disinfect with 1000 ppm bleach	B—II
Laboratory diagnosis for CDI	
Only check unformed stool samples	B—II
Use *C. difficile* specific commercial kits	
EIA toxin assay	B—II
EIA GDH and toxin assay	B—II
tcdB PCR detection	B—II
Do stool culture for *C. difficile*	A—II
Therapy for CDI	
Avoid unnecessary antibiotics	A—II
Oral metronidazole for mild CDI	A—I
Oral vancomycin for severe CDI	B—I
Oral vancomycin for CDI with >1 recurrence	B—III

EIA = enzyme immunoassay; GDH = glutamate dehydrogenase; PCR = polymerase chain reaction.

coefficient alpha of the study was 0.63, indicative of acceptable reliability of internal consistency. Their mean age was 43.2 ± 10.0 (range: 18—81) years old, with 182 (44.9%) aged between 30 and 40 years and 118 (29.1%) between 40 and 50 years. Most participants were physicians (169, 38.3%) and nurses (115, 26.1%). Their seniorities were in average 10.1 years, less than 5 years in 47.2% of the participants, and between 10 and 20 years in 22.2%.

For the awareness of infection control measures in their hospital, 280 (63.5%) participants reported there was routine monitoring of CDI, and 347 (78.7%) knew several infection control policies implemented, including contact isolation (75.7%), wearing gloves (88.9%) or dressing (80.0%), if the hospital staffs cared CDI patients, single room isolation (49.7%), the use of soap or disinfectant-based hand antiseptic (83.2%), avoidance of alcohol-based sanitizers (63.3%), and environmental disinfection with 1000 ppm bleach (87.1%), as noted in Fig. 1. For the timing of discontinuation of contact isolation, 39.9% of the participants would wait until the absence of *C. difficile* toxin in stool from the cases of CDI. Only less than 1/3 (32.7%) of participants would stop contact precaution until diarrhea resolution for at least 48 h, and 15.2% would discontinue isolation immediately after diarrhea resolved (Table 3).

To diagnose CDI, a half of participants reported no specific tests utilized in their hospitals, and (40.6%) participants reported PCR or nucleic acid amplification tests (NAATs) targeting *C. difficile* toxin-related genes, followed by EIA kits targeting *C. difficile* toxin (4.8%) and glutamate dehydrogenase (3.6%, Fig. 2). Only 199 (45.1%) participants acknowledged stool cultures for *C. difficile*, in addition to the above specific tests, and reported that selective media for *C. difficile* growth was rarely used, including cycloserine-cefoxitin-fructose agar (12.0%) or *C. difficile*

Table 2 Basic characteristics of the participants from different healthcare facilities.

Variables	Total N = 441	Medical centers N = 103	District hospitals N = 114	Regional hospitals N = 103	Clinics N = 30	Others N = 91	*P* value
Gender, male	176 (39.9)	54 (52.4)	51 (44.7)	23 (22.3)	14 (46.7)	34 (37.4)	0.001
Age							0.30
≤30 years	24 (5.9)	2 (2.1)	9 (8.3)	9 (9.7)	1 (3.7)	3 (3.7)	
30—40 years	182 (44.9)	39 (41.5)	49 (45.0)	43 (46.2)	13 (48.1)	38 (46.3)	
40—50 years	118 (29.1)	34 (36.2)	38 (34.9)	20 (21.5)	6 (22.2)	20 (24.4)	
50—60 years	57 (12.9)	15 (14.6)	9 (7.9)	13 (12.6)	5 (16.7)	15 (16.5)	
>60 years	24 (5.4)	4 (3.9)	4 (3.5)	8 (7.8)	2 (6.7)	6 (6.6)	
Missing data	36 (8.2)	9 (8.7)	5 (4.4)	10 (9.7)	3 (10.0)	9 (9.9)	
Occupation							<0.001
Physicians	169 (38.3)	59 (57.3)	53 (46.5)	23 (22.3)	12 (40.0)	22 (24.2)	
Nurses	115 (26.1)	14 (13.6)	34 (29.8)	45 (43.7)	2 (6.7)	20 (22.0)	
Medical technologists	37 (8.4)	9 (8.7)	15 (13.2)	5 (4.9)	2 (6.7)	6 (6.6)	
Pharmacists	3 (0.7)	0	1 (0.9)	0	1 (3.3)	1 (1.1)	
Others	117 (26.5)	21 (20.4)	11 (9.6)	30 (29.1)	13 (43.3)	42 (46.2)	
Seniorities							0.23
≤5 years	208 (47.2)	37 (35.9)	55 (48.2)	57 (55.3)	18 (60.0)	41 (45.1)	
5—10 years	59 (13.4)	17 (16.5)	12 (10.5)	15 (14.6)	3 (10.0)	12 (13.2)	
10—20 years	98 (22.2)	32 (31.1)	30 (26.3)	15 (14.6)	3 (10.0)	18 (19.8)	
20—30 years	34 (7.7)	9 (8.7)	8 (7.0)	7 (6.8)	1 (3.3)	9 (9.9)	
Missing data	42 (9.5)	8 (7.8)	9 (7.9)	9 (8.7)	5 (16.7)	11 (12.1)	

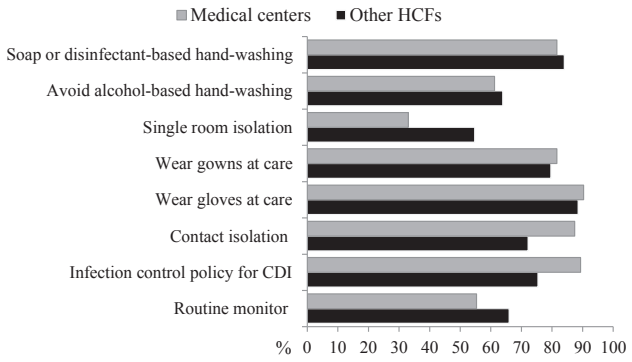

Figure 1. Infection control measures adopted in clinical care of the cases of *Clostridium difficile* infection (CDI) in medical centers or other healthcare facilities (HCFs).

selective agar (6.3%). Most participants recognized that attending clinicians (76.4%) or infection control team (76.6%) will be informed for positive *C. difficile* results by the laboratory staffs.

As for clinical management or treatment of CDI, 326 (73.9%) participants would not treat asymptomatic carriers, but only 212 (48.1%) would avoid unnecessary antibiotics (Table 3). For the patients with mild CDI, most (61.9%) participants would recommend oral metronidazole, and severe CDI would be first managed by intravenous metronidazole (26.3%) or oral vancomycin (26.1%, Fig. 3). For the patients with the first recurrent CDI, most (44.7%) participants would select oral vancomycin as the drug of choice, and for those with more than one recurrence, 23.8% and 23.1% would choose oral vancomycin and intravenous metronidazole, respectively, as the drug of choice. Probiotics may be used for refractory or recurrent CDI in 62.8% of participants. Of note, 221 (50.1%) would consider fidaxomicin which was not marketed in Taiwan yet, for refractory CDI (Table 3).

As for the perceptions of infection control measurements for CDI, infection control nurses more often reported single room isolation (66/115, 57.4% *vs.* 67/169, 39.6%, $P = 0.002$) and the avoidance of alcohol-based hand washing (86/115, 74.8% *vs.* 100/169, 59.2%, $P = 0.02$) than infection disease specialists. In contrast, infection disease

Table 3 Clinical management of *Clostridium difficile* infection (CDI) between infection control professionals from medical centers or other healthcare facilities.

Clinical management	Total N = 441	Medical centers		*P* value
		No, N = 338	Yes, N = 103	
Time to discontinue isolation for patients with CDI				0.05
Immediately after diarrhea resolution	67 (15.2)	47 (13.9)	20 (19.4)	
Diarrhea resolution for at least 48 h	144 (32.7)	102 (30.2)	42 (40.8)	
Stool negative for *C. difficile* toxin	176 (39.9)	147 (43.5)	29 (28.2)	
Never stop isolation	9 (2.0)	7 (2.1)	2 (1.9)	
Unclear	45 (10.2)	35 (10.4)	10 (9.7)	
Disinfect environment with 1000 ppm bleach	384 (87.1)	291 (86.1)	93 (90.3)	0.18
Only check unformed stool samples	135 (30.6)	95 (28.1)	40 (38.8)	0.09
Inform clinicians for positive results	337 (76.4)	254 (75.1)	83 (80.6)	0.21
Inform infection control team for positive results	338 (76.6)	252 (74.6)	86 (83.5)	0.06
Do stool culture for *C. difficile* in addition to kit	199 (45.1)	145 (42.9)	54 (52.4)	0.02
Do not treat asymptomatic carriers	165 (37.4)	119 (35.2)	46 (44.7)	0.08
Avoid unnecessary antibiotics	326 (73.9)	255 (75.4)	71 (68.9)	0.19
Prescribe probiotics for refractory/recurrence CDI	277 (62.8)	218 (64.5)	59 (57.3)	0.02
Consider fidaxomicin in refractory CDI	221 (50.1)	167 (49.4)	54 (52.4)	<0.001

Note: EIA: enzyme immunoassay; PCR: polymerase chain reaction.

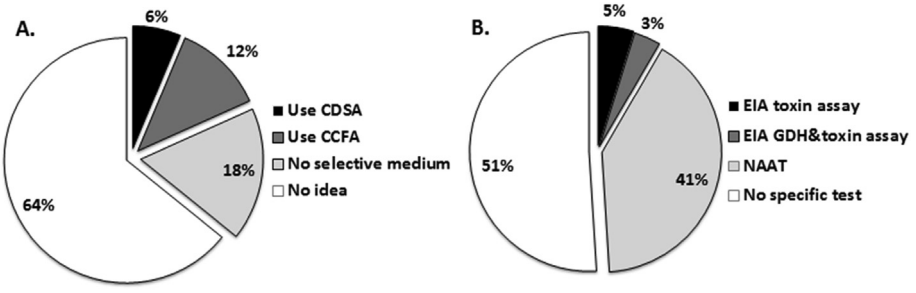

Figure 2. Perceptions of culture media (A) and diagnostic tests (B) of *Clostridium difficile* infections in clinical laboratories. Note: CDSA = *Clostridium difficile* selective agar; CCFA = cycloserine-cefoxitin-fructose agar; EIA = enzyme immunoassay; GDH = glutamate dehydrogenase; NAAT = nucleic acid amplification test.

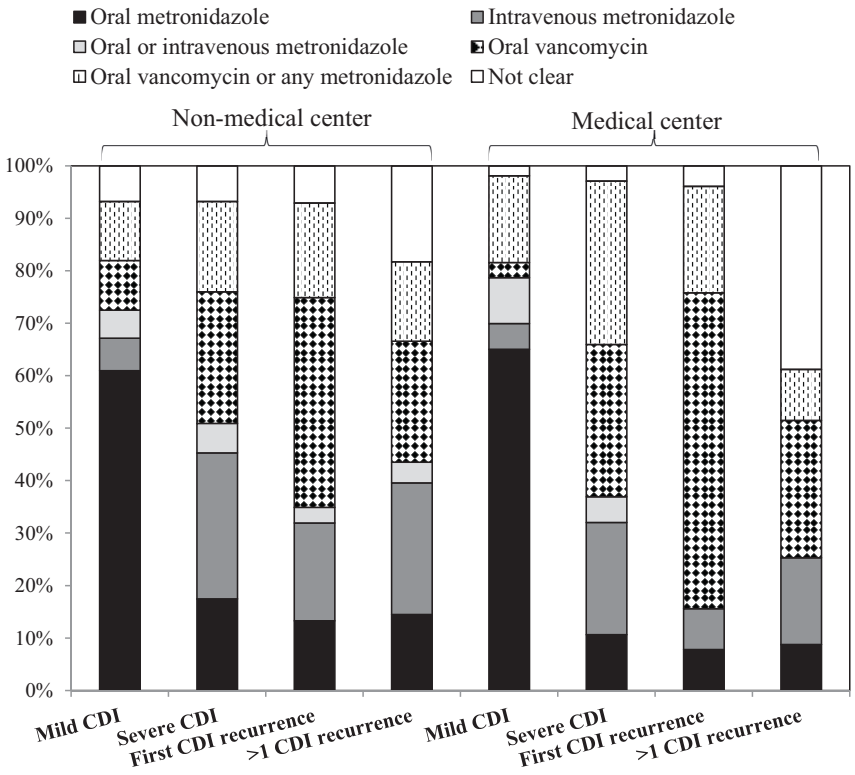

Figure 3. Therapeutic choices of a variety of severity spectrum of *Clostridium difficile* infection (CDI) among the participants from medical centers or other healthcare facilities.

specialists would be more likely to test unformed stool samples for *C. difficile* infection (71/169, 42.0% *vs.* 33/115, 28.7%, $P = 0.007$), to select oral metronidazole for mild CDI (127/169, 75.1% *vs.* 66/115, 57.4%, $P < 0.001$), oral vancomycin for severe CDI (67/169, 39.7% *vs.* 19/115, 16.5%, $P < 0.001$), and to consider fidaxomicin for refractory CDI (101/169, 59.8% *vs.* 45/115, 39.1%, $P < 0.001$), as compared with infection control nurses.

Discussion

Though the guidelines about CDI had been proposed for several years,[9,10] this is the first paper disclosing the perceptions of CDI among infection control professionals in Taiwan. These results revealed the gap between international consensus and current concepts and practices in Taiwan. The recommendation that only unformed stools could be accepted for *C. difficile* testing has been widely adopted in many clinical laboratories, because there are asymptomatic carriers of *C. difficile*, for who no treatment is needed.[9,10] Likewise, our previous work found up to 20% of hospitalized adults had *C. difficile* colonization, without diarrheal illness at initial screening in Taiwan.[13] It is surprising that 70% of the participants will test for *C. difficile* infection in formed stool from patients without diarrhea. With positive results of *C. difficile* testing for asymptomatic individuals, over-diagnosis of CDI might result in the unnecessary prescription of antimicrobial agents and implementation of infection control measures.

To obtain laboratory evidences of CDI, most (60%) of infection control professionals in medical centers reported the application of PCRs, EIA targeting glutamate dehydrogenase (GDH) and/or *C. difficile* toxin. Nucleic acid amplification testing provides high sensitivity and specificity, both higher than 90% in detecting toxigenic *C. difficile*. Nevertheless, this method may identify asymptomatic carriers of toxigenic *C. difficile* and thus some experts would debate against PCR-based testing alone.[10,14,15] Though multistep algorithms to diagnosis CDI had been suggested,[9,10,16] many participants in Taiwan reported that there was no specific test available for CDI. To increase the availability of at least one laboratory test, either EIA or NAAT, to facilitate the clinical diagnosis of CDI in the clinics and hospitals, is urgent in the era of increasing antibiotic resistance among human pathogens.

It is well documented that clinical cure rate for metronidazole and vancomycin therapy was not different (90% *vs.* 98%, respectively) among patients with mild CDI, and for severe CDI, that of vancomycin therapy was higher than that of metronidazole regimen (97% *vs.* 76%).[17] However in our study some (20.4%) participants might prescribe vancomycin for mild CDI, and only 26.1% of participants would give oral vancomycin as the drug of choice for severe CDI. Furthermore, vancomycin had been suggested for CDI patients with more than one recurrence, because metronidazole was not suggested for long-term therapy with the concern of cumulative neurotoxicity.[18] Less than half (23.8%) of the participants would choose vancomycin for recurrent CDI. Education programs to optimize the therapeutic efficacy of antimicrobial therapy for the treatment CDI in Taiwan are urgently needed.

There are some limitations in our study. Firstly we delivered our questionnaire in the annual meeting of IDST and ICST of Taiwan, and not all members were assessed for their will for participation. Therefore, the response rate among all infection control professionals in Taiwan cannot be estimated. Secondly, there could be several participants responding to the questionnaire from one hospital or healthcare facility, the data of the specific types of laboratory tests to diagnose CDI cannot truly reflect current popularity of varied diagnostic modalities in Taiwan hospitals. Thirdly, some participants did not provide personal information, such as age, occupation, or service setting, and the impact of these variables on each question was obscured. Nevertheless this was the first survey regarding the knowledge of infection control practices or therapeutic regimens toward CDI in Taiwan. These results may be used as the references in the designs of training programs and working guidelines for medical professionals in Taiwan.

In conclusion, there were discordances of infection control polices and therapeutic choices for CDI between international guidelines and the perceptions of medical professionals in Taiwan. More education programs and the need of clinical management consensus for CD should be considered in Taiwan.

Conflicts of interest

All authors had no conflicts of interest.

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