DEPARTMENT OF VETERANS AFFAIRS
Veterans Health Administration
Washington DC 20420

IL 10-2005-018
In Reply Refer To: 111

September 8, 2005

UNDER SECRETARY FOR HEALTH'S INFORMATION LETTER

CLOSTRIDIUM DIFFICILE (C. difficile)

1. Background

a. *Clostridium difficile* is a spore-forming gram-positive anaerobic bacillus that produces exotoxins and causes gastrointestinal infections in humans, and is shed in feces. The range of infections in humans can be from asymptomatic colonization to severe disease, including diarrhea, pseudomembranous colitis, toxic megacolon, colonic perforation, and death. Morbidity can range from discomfort or embarrassment due to diarrhea to severe septic illness and colectomy with resultant colostomy. It is likely to be the most frequently-identified cause of health care-associated diarrhea. Disease due to *C. difficile* comes from the production of cytotoxic exotoxins (Toxin A and Toxin B) that adversely affect the mucosa of the large bowel; these adverse affects then lead to the previously mentioned clinical conditions. The presence of toxin is a marker for disease.

b. Recent analysis of discharge records from within the VHA nationwide for Fiscal Year (FY) 2004 indicate that about 1 percent of all hospital discharges contained an Internatonal Classification of Diseases, Clinical Modification, 9th edition (ICD-9-CM)-coded diagnosis for *C. difficile* infection (see Att. B). Multiple studies have shown that acquisition of *C. difficile*, in both symptomatic and asymptomatic forms, does occur in the health care setting. Further, contamination of the hospital environment (with *C. difficile* in both vegetative and spore form) and hands of health care personnel occurs frequently. In particular, *C. difficile* in the spore state is resistant to a number of routine environmental cleaning, sanitization, and disinfection methods employed in health care, thus making transmission more likely.

2. Clinical Issues

a. It is widely accepted that *C. difficile* is the primary pathogen responsible for antibiotic associated colitis, and up to 25 percent of cases of antibiotic-associated diarrhea. While it is not entirely clear what the carriage rate or colonization rate for *C. difficile* is in the population, studies have shown a wide range of asymptomatic carriage from at least 2-15 percent. Acquisition of the organism during hospitalization also varies widely, but can be as high as 20 percent with most remaining asymptomatic.

b. It is not clear what the prevalence of *C. difficile* infection is in asymptomatic patients in hospital settings; however, in at least one study, it has been found in 30 percent of adult patients who develop diarrhea during hospitalization. It is a particularly common cause of health care-associated diarrhea that occurs after 72 hours of hospitalization. While most cases appear to be related to the hospital setting, freestanding hospital-like settings where antibiotics are used may also be important. Community-acquired infection and disease in healthy, ambulatory populations is uncommon.

c. The major risk factor for acquisition of *C. difficile*-associated infection is use of antimicrobial agents. While clindamycin was the antibiotic most commonly noted in the early studies of *C. difficile* colitis and antibiotic-related diarrhea, other antibiotics are currently more often associated with *C. difficile* infection. The use of multiple antimicrobial agents may put patients at a higher risk of developing disease due to *C. difficile*. Even short course antimicrobial therapy for indications, such as antimicrobial prophylaxis for surgery, can trigger antibiotic-associated colitis related to *C. difficile*. In addition, *C. difficile* virulence, antibiotic resistance, and use of proton pump inhibitors have recently been discussed as risk factors. The route of transmission for *C. difficile* is not entirely clear, but is likely related to persons infected with the organism, environmental contamination including inanimate objects, and the carriage of the organism on the hands of those persons in contact with contaminated material, objects or environment. Any surface, device, or material (e.g., commodes, bathing tubs, and electronic rectal thermometers) that becomes contaminated with infected feces may serve as a reservoir for *C. difficile* spores.

3. Diagnosis. *C. difficile*-associated gastrointestinal disease should be suspected in hospitalized patients with new onset diarrhea after admission, particularly those patients who have received antibiotics or have had a disruption of the normal gastrointestinal tract flora prior to the onset of diarrhea. In general, the stool is tested for evidence of *C. difficile* toxin rather than culture of the organism. There are a number of assays available to test for *C. difficile* toxins. It is important to know the assay being used by the laboratory where the stool specimens are sent for this testing, as some assays detect only one toxin (usually Toxin A) and there are uncommon situations where Toxin B is the predominant toxin excreted. Even though culture is not routinely done for isolation of *C. difficile*, its use in well-defined epidemiological investigations may be quite important either with respect to evaluation of spread of clonal strains within an institution, or for evaluation of the presence of one of the more virulent outbreak strains that have recently been described in the United States These virulent strains appear to cause more serious disease, so presence of the strain may indicate the need for more stringent control measures to prevent further transmission.

4. Treatment. Treatment of symptomatic *C. difficile* colitis involves a multifaceted approach. If possible, discontinuation of antimicrobial agents currently being used to treat the patient is recommended. By removing a predisposing factor or insult, it allows the re-establishment of normal bowel flora. *C. difficile* antibiotic-related diarrhea often ceases with discontinuation of these antibiotics. However, for many cases, discontinuation of antibiotics alone will not result in cessation of diarrhea. Further, some patients need to continue antibiotic therapy, which provides

a stimulus for continued *C. difficile* colitis. Additionally, some experts advocate aggressive treatment of *C. difficile*, in conjunction with removal of antibiotic agents. In such cases, metronidazole is currently the recommended treatment. Oral or enteral delivery is preferred. The most recent guidelines from the Centers for Disease Control and Prevention, the Society of Healthcare Epidemiology of America, the Infectious Diseases Society of America, the American College of Gastroenterologists, the American Gastroenterological Association and the American Society of Health Systems Pharmacists need to be used to ensure the most up-to-date therapeutic intervention for this illness. Oral vancomycin is an effective agent, but in general, should not be the first line of therapy because of the theoretical potential for oral vancomycin to lead to increased incidence of vancomycin-resistant enterococcus in the health care setting. Indications for use of oral vancomycin include persistent *C. difficile* colitis or diarrhea despite several full course treatments with metronidazole and the removal of inciting antibiotics, allergy or intolerance to metronidazole, and severe or life-threatening *C. difficile* disease. For clinical situations where severe toxic megacolon is suspected, some have advocated the use of vancomycin or metronidazole containing enema solutions for direct colonic mucosal contact with the treating agent; however, these modalities have not been well studied, and their effectiveness is unproven. The addition of parenteral metronidazole to an oral or enteral regimen has also been advocated for illness where paralytic ileus may be present, but again, clear effectiveness has not been proven. Surgical intervention with decompression and/or colectomy may be a therapeutic option for severe disease. Treatment of asymptomatic persons colonized with *C. difficile* is generally not recommended. For persons who have a first recurrence of *C. difficile* diarrhea after appropriate therapy, treatment should be repeated using the same drug as the initial episode, (i.e., metronidazole in most cases).

5. <u>Prevention and Control.</u> As noted, *C. difficile* is presumably transmitted by contact; the spores formed by this agent create a means of persistence in the environment from which continued transmission may occur. Principles of prevention and control needs to be focused on strategies that minimize or reduce the likelihood of surface (both patient and environment) contamination with *C. difficile* in either vegetative or spore form.

a. There are compelling clinical data that the proper use of gloves by personnel for handling body substances and inanimate objects in the environment may interrupt transmission of *C. difficile* from patient to patient.

b. Use of contact precautions and a private room for patients with *C. difficile*-associated diarrhea is recommended. Preferably, the private room needs to have a private toilet facility associated with it. If private rooms are not available, priority for such rooms needs to be for patients who cannot maintain bowel continence and good hand hygiene. Cohorting of patients may be needed should private rooms and toileting facilities not be available. The mechanism for cohorting depends upon a number of institution-specific features, including: room locations and nursing staffing, availability of toileting facilities, and presence of an outbreak within the institution (including possible virulent strain introduction). Decisions about how best to cohort should be made on a local basis with active input from the infection control professional, hospital epidemiologist, infectious diseases physicians, and nurse managers responsible for the care of patients on the wards where cohorting will occur.

c. Antimicrobial use guidelines and restrictions may be helpful in settings where specific antimicrobial use is a risk for *C. difficile*-associated diarrhea. This may be institution-specific based on antimicrobial usage, underlying diseases of patients, and prevalence of *C. difficile* in the population. Overall antibiotic stewardship programs are an integral component of prevention of *C. difficile* colitis.

d. The issue of hand hygiene is important. Since *C. difficile* is a spore-forming organism, it is not clear that alcohol-based handrubs are effective in eliminating the organism from the hands. As such, relative to care delivered by the health care team to persons suffering from *C. difficile* disease, the current recommendation is for the use of gloves and traditional hand washing with either an antimicrobial agent or soap after contact with patients, their body substances, or environmental surfaces in rooms where patients with *C. difficile*-associated diarrhea are housed or where contact with such patients occurs.

e. If *C. difficile* rates are high, replacement of rectal electronic thermometers with disposable rectal thermometers is recommended

f. There is controversy as to whether the environment is a source of patient infection or is merely contaminated as a result of occupancy by a *C. difficile* infected patient. Despite this controversy, many experts strongly feel that environmental contamination needs to be addressed. Few studies have examined the use of specific chemical germicides for the inactivation of *C. difficile* spores, and no well-controlled trials have been conducted to determine efficacy of surface disinfection and its impact on health-care-associated diarrhea. Some investigators have evaluated the use of chlorine-containing chemicals (e.g., 1,000 ppm hypochlorite at recommended use-dilution, 5,000 ppm sodium hypochlorite [1:10 v/v dilution], 1:100 v/v dilutions of unbuffered hypochlorite, and phosphate-buffered hypochlorite [1,600 ppm]) with varying reported results. Disadvantages to the routine use of hypochlorite-based products include corrosion of surfaces, low tolerance to inorganic matter, odor, and reduced effectiveness in cleaning surfaces. Environmental Protection Agency (EPA)-registered hospital disinfectants are recommended for general use whenever possible in patient-care areas. However, in circumstances where transmission of *C. difficile* is of concern, consider the use of an EPA-registered hypochlorite-based disinfectant for environmental surface disinfection after cleaning in accordance with label instructions; generic sources of hypochlorite (e.g., household chlorine bleach) may also be appropriately diluted and used. When transferring chemicals from original labeled containers, any subsequent labeling requirements need to be in compliance with 29 Code of Federal Regulations (CFR) 1910.1200 Hazard Communication. When there is concern regarding *C. difficile*, the CDC-recommended approach to environmental infection control is meticulous cleaning followed by disinfection using hypochlorite-based germicides, as appropriate.

6. <u>Conclusion.</u> Complete elimination of *C. difficile*-associated diarrhea in the health care setting is unlikely. It is incumbent on the institution to adopt stringent institutional practices that minimize the potential for spread and transmission of *C. difficile* within health care facilities. Certain recommendations have evidence-based rationale and should warrant inclusion in a

hospital or health care infection control program. These include the appropriate use of all antibiotics, early identification of *C. difficile*-associated diarrhea, and contact precautions for such patients, early therapy as appropriate for each patient with *C. difficile*-associated diarrhea, rigorous adherence to the appropriate use of gloves, and the need for hand washing in the setting of *C. difficile* disease. Lastly, thorough cleaning of rooms that have housed patients with *C. difficile* diarrhea (and of all items used in the rooms of patients with *C. difficile*-associated diarrhea) needs to be accomplished to prevent transmission to the next occupant of the facility.

S/Jonathan B. Perlin, MD, PhD, MSHA, FACP
Under Secretary for Health

DISTRIBUTION: CO: E-mailed 9/14/05
FLD: VISN, MA, DO, OC, OCRO, and 200 – E-mailed 9/14/05

ATTACHMENT A

REFERENCES

1. Brooks, SE. "Reduction in the Incidence of *Clostridium difficile*-associated Diarrhea in an Acute Care Hospital and a Skilled Nursing Facility Following Replacement of Electronic Thermometers with Single-use Disposables," Infection Control and Hospital Epidemiology 13:98-103; 1992.

2. CDC. "*Clostridium difficile* Information for Health Care Providers," Fact Sheet. http://www.cdc.gov/ncidod/hip/gastro/ClostridiumDifficileHCP_print.htm dated August 2004 and Updated 9/23/04.

3. CDC. "Guidelines for Environmental Infection Control in Health-Care Facilities. Recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee (HICPAC)," Morbidity and Mortality Weekly Report (MMWR). 52, RR-10; 2003. http://www.cdc.gov/mmwr/PDF/rr/rr5210.pdf

4. CDC. "Guideline for Hand Hygiene in Health-Care Settings. Recommendations of the Healthcare Infection Control Practices Advisory Committee and the HICPAC/SHEA/APIC/IDSA Hand Hygiene Task Force," MMWR 51(RR-16); 2002. http://www.cdc.gov/mmwr/PDF/rr/rr5116.pdf

5. Chou, T. Environmental Services. Association for Professionals in Infection Control and Epidemiology, Inc. APIC Text of Infection Control and Epidemiology, 2nd Ed., Chapter 102; 2005.

6. Dial, S. Alrasadi, K. Manoukian, C., Huang, A., Menzies, D. "Risk of *Clostridium difficile* Diarrhea Among Hospital Inpatients Prescribed Proton Pump Inhibitors; Cohort and Case-control Studies," Canadian Medical Association Journal. Vol. 171(1); 2004. http://www.cmaj.ca/cgi/content/full/171/1/33

7. Gerding, D.N. "Clindamycin, Cephalosporins, Fluoroquinolones, and *Clostridium difficile*-Associated Diarrhea: This Is an Antimicrobial Resistance Problem," Editorial Commentary. Clinical Infectious Diseases Vol. 38:646-648; 2004.

8. Gerding, D.N., Johnson, S., Peterson, L.R., Mulligan, M.E., Silva, J. "*Clostridium-difficile*-Associated Diarrhea and Colitis," SHEA Position Paper. Infection Control and Hospital Epidemiology. Vol. 16:459-477; 1995.

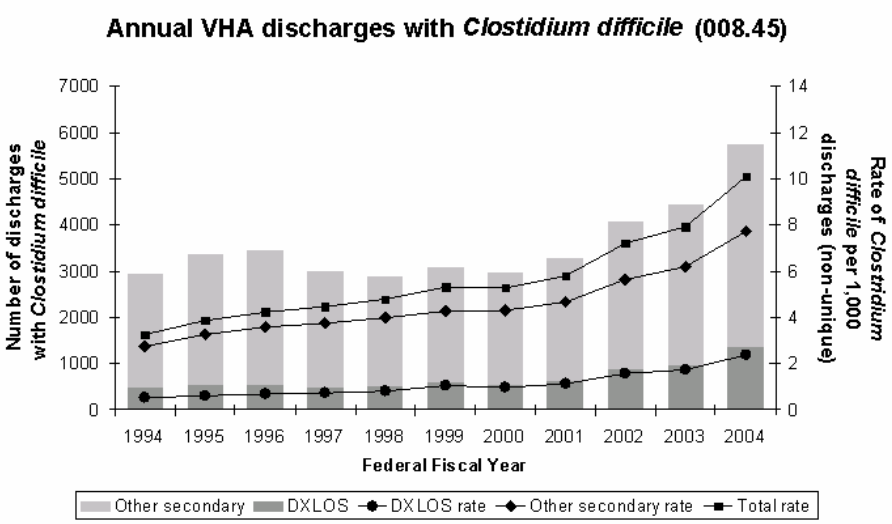
9. Gerding, D.N. Pseudomembranous Colitis (*Clostridium difficile*). Association for Professionals in Infection Control and Epidemiology, Inc. APIC Text of Infection Control and Epidemiology, 2nd Ed., Chapter 75; 2005.

10. Johnson, S., Gerding, D.N. Chapter 36, *Clostridium difficile*, published in Hospital Epidemiology and Infection Control. 3rd ed. C.G. Mayhall (editor) pgs. 628-630, Lippincott Williams & Wilkins, Philadelphia, PA. 2004.

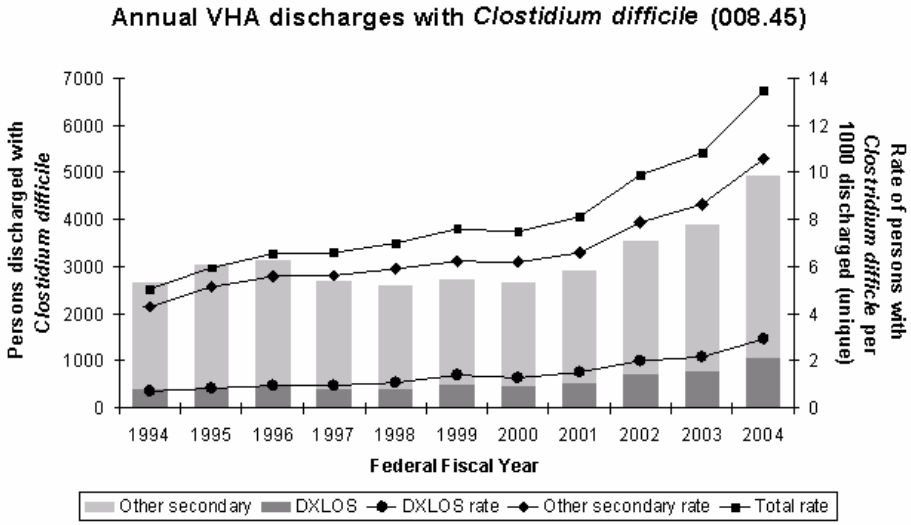
11. Loo, V.G., Libman, M.D., Miller, M.A., Bourgault, A.M., Frenette, C.H. Kelly, M., Michaud, S., Nguyen, T., Poirier, L., Vibien, A., Horn, R., Laflamme, P.J., Rene′, P. "*Clostridium difficile*: a Formidable Foe," Canadian Medical Association Journal 171(1), 2004. http://www.cmaj.ca/cgi/content/full/171/1/47

12. Simor, A.E., Bradley, S.F., Strausbaugh, L.J., Crossley, K., Nicolle, L.E., the SHEA Long-Term-Care Committee. "*Clostridium difficile* in Long-Term-Care Facilities for the Elderly," SHEA Position Paper. Infection Control and Hospital Epidemiology 23:696-703; 2002.

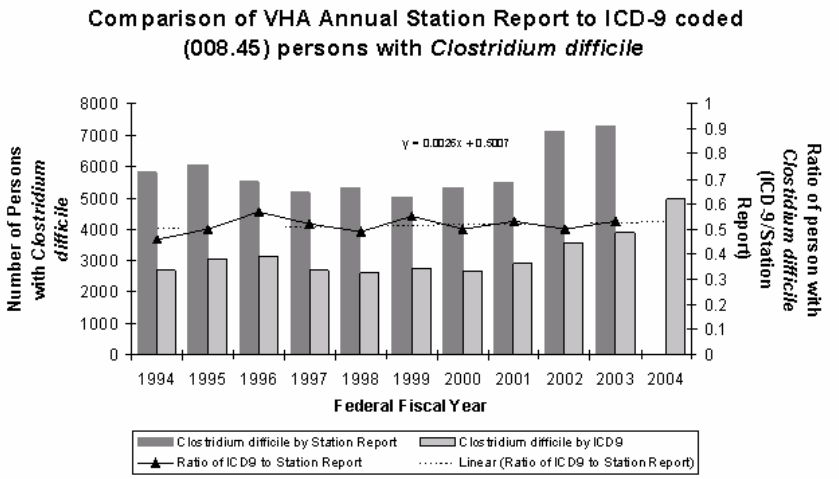
ATTACHMENT B



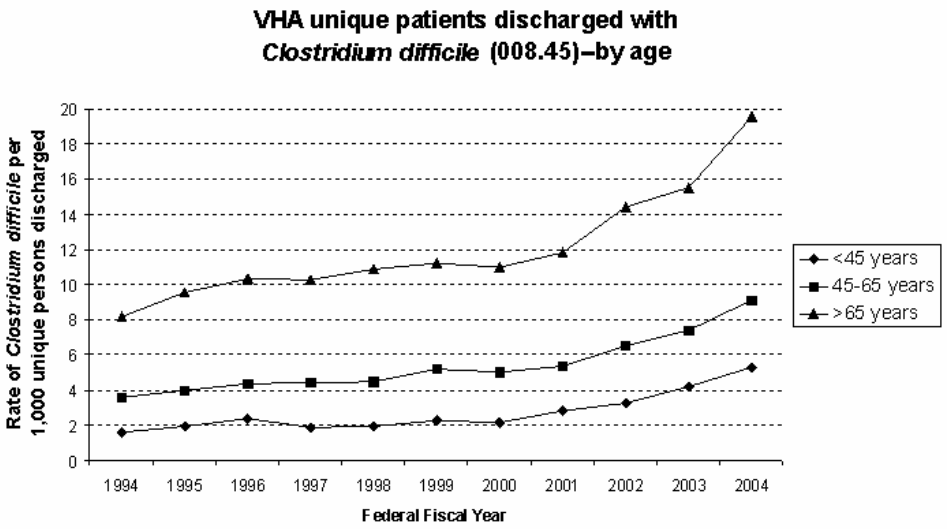
A. This figure has been derived from information available from the Patient Treatment Files (PTF), for inpatient encounters, nationwide for the VHA system. This looks at all discharges to determine whether an ICD-9 diagnosis code for *Clostridium difficile* (008.45) was present; as such it represents burden of disease to the healthcare system of VHA nationwide. The bar graphs represent actual numbers of discharges with an ICD-9 of 008.45 present (the darker gray is the number that had 008.45 as the diagnosis-length of stay [DXLOS] and the lighter gray is the number that had 008.45 as a secondary diagnosis). The line graphs represent a rate of discharges where *Clostridium difficile* (008.45) was present as a function of all discharges from VA Medical Centers nationwide.



B. This figure has been derived from information available from the Patient Treatment Files (PTF), for inpatient encounters nationwide for the VHA system. It is similar to graph A, but rather than looking at all discharges, this graphic looks at all patients discharged (i.e. burden of disease relative to patients rather than burden of disease to the healthcare system). This looks at all patients discharged as a unique finding (a patient will only be counted once in this analysis regardless of how many times discharged during the year or regardless of how many discharges had a diagnosis of *Clostridium difficile* infection). As in Graph A, analysis was performed to determine whether an ICD-9 diagnosis code for *Clostridium difficile* (008.45) was present. The bar graphs represent actual numbers of persons who had at least one discharge during the year with an ICD-9 of 008.45 present (the darker gray is the number that had 008.45 as the diagnosis-length of stay [DXLOS] and the lighter gray is the number that had 008.45 as a secondary diagnosis). The line graphs represent a rate of persons where *Clostridium difficile* (008.45) was present as a function of the number of (unique) persons discharged from VA Medical Centers nationwide.



C. This figure has been derived from information available from the Patient Treatment Files (PTF), for inpatient encounters nationwide for the VHA system (administered by the Austin Automation Center) and from information available from the Infectious Diseases/Infection Control Annual Station Report (administered by VA Central Office Infectious Diseases Program). This graphic uses ICD-9 coded discharges for *Clostridium difficile* (008.45) from the PTF files (light gray bars) and it uses the number of persons who had stool positive (not tests) for *Clostridium difficile* toxin from the Annual Station Report (dark gray bars). This looks at all patients as a unique finding (a patient will only be counted once in this analysis regardless of how many times discharged during the year or regardless of how many discharges had a diagnosis of *Clostridium difficile* infection or regardless of how many times a patient had a stool positive for *Clostridium difficile* toxin). A ratio of number of persons with Clostridium difficile reported by ICD-9 compared to number of persons reported by Annual survey is provided (line graph) to estimate possible underreporting of *Clostridium difficile* disease by ICD-9 coded diagnosis. Despite increases in numbers of cases in the last several years, the ratio of ICD-9 reported cases to Annual Station Report reported cases is consistently about 0.53; this indicates that ICD-9 coding reports about 50% of the number of persons noted an the annual station report to have stool positive for *Clostridium difficile* toxin.



D. This figures has been derived from information available from the Patient Treatment Files (PTF), for inpatient encounters nationwide for the VHA system. A subset analysis of rate of *Clostridium difficile* disease by age-matched group was performed. As in figure B, this looks at all patients discharged as a unique finding (a patient will only be counted once in this analysis regardless of how many times discharged during the year or regardless of how many discharges had a diagnosis of *Clostridium difficile* infection). As you will note, incidence of disease increases with increasing age.