



Pennsylvania Patient Safety Reporting System

# Patient Safety Advisory

Produced by ECRI & ISMP under contract to the Pennsylvania Patient Safety Authority

## Clostridium Difficile: A Sometimes Fatal Complication of Antibiotic Use

### “C. diff”: What Is It?

Technically, *Clostridium difficile* (C. diff) is a bacteria in the Clostridia family, which also includes *C. perfringens* (gas gangrene), *C. tetani* (tetanus), and *C. botulinum* (botulism). The Clostridia bacteria are spore-forming anaerobic gram positive bacilli which are particularly virulent because of the toxins they produce.

Clinically, “C. diff” refers to an overgrowth of *C. difficile* in the colon which can manifest as diarrhea, sometimes profound, colitis, or toxic megacolon, sometimes complicated by dehydration, colonic perforation, and/or death. The overgrowth of *C. diff* in the colon usually results from alterations in the normal colonic flora associated with use of antibiotics.

### A Serious Problem Reported to PA-PSRS

*C. diff* is documented in almost half the reports submitted to PA-PSRS under the Event Type code “Nosocomial infection: antibiotic-associated diarrhea.” However, of greatest concern is the number of reports involving patient deaths in which *C. diff* is mentioned as a major contributing factor. PA-PSRS has received 15 such reports to date. Diagnoses include sepsis/septic shock, toxic megacolon, colitis, diarrhea, and abdominal pain. Most patients in these reports (86%) were age 70 or older.

Several reports indicate that patients treated with antibiotics prophylactically for an elective surgical procedure developed symptoms of *C. diff* infection in the community after discharge. They failed to return to the healthcare system until their disease had progressed significantly. From the patient’s perspective, the relatively routine nature of the surgery in several cases (e.g., knee replacement, repair of a hip or ankle fracture, hysterectomy) may have obscured the connection between the gastrointestinal symptoms of *C. diff* infection and their recent treatment.

The following reports submitted to PA-PSRS illustrate this point.

*A 72-year-old patient came to the ED complaining of a near syncopal episode. He had been discharged two weeks before, after being treated for community-acquired pneumonia. He was taking an*

*antibiotic upon discharge and finished the full course of medication at home. The patient also complained of diarrhea, nausea, and abdominal discomfort over the previous week. The patient arrived, in fact, in septic shock. Fecal testing was positive for C. diff. Despite aggressive intervention, the patient died of C. diff sepsis within 16 hours of returning to the ED.*

*An 87-year-old patient was discharged to a rehabilitation facility after repair of a hip fracture and receipt of antibiotic therapy. Eighteen days later, the patient returned to the hospital in septic shock associated with C. diff. The patient died the day she returned to the hospital despite aggressive intervention.*

### The Bottom Line

The message for the healthcare community is to avoid complacency about the risk of *C. diff* infection and to help patients to understand when they need to return to the healthcare system for additional treatment, especially for diarrhea complicating antibiotic use. The risks of surgical complications may overshadow the risks of prophylactic antibiotics not only in the minds of patients and their families but also among healthcare workers.

### C. Diff Infections

While much attention has been focused on such hospital-acquired infections as MRSA (Methicillin-resistant *Staphylococcus aureus*) and VRE (Vancomycin-resistant enterococcus), *C. diff* has become a growing concern. *C. diff*-associated diseases cause significant morbidity and mortality. Patients

This article is reprinted from the *PA-PSRS Patient Safety Advisory*, Vol. 2, No. 2—June 2005. The Advisory is a publication of the Pennsylvania Patient Safety Authority, produced by ECRI & ISMP under contract to the Authority as part of the Pennsylvania Patient Safety Reporting System (PA-PSRS).

Copyright 2005 by the Patient Safety Authority. This publication may be reprinted and distributed without restriction, provided it is printed or distributed in its entirety and without alteration. Individual articles may be reprinted in their entirety and without alteration provided the source is clearly attributed.

To see other articles or issues of the Advisory, visit our web site at [www.psa.state.pa.us](http://www.psa.state.pa.us). Click on “Advisories” in the left-hand menu bar.

## Clostridium Difficile: A Sometimes Fatal Complication of Antibiotic Use (Continued)

with *C. diff*-associated diarrhea (CDAD) have hospital stays that are, on average, 3.6 days longer, and each patient results in additional hospital costs of an average of \$3,669.<sup>1</sup> A conservative estimate of the cost of this disease in the US is over \$1 billion annually.<sup>1</sup>

In its spore form, *C. diff* can withstand drying and heat, and is resistant to many disinfectants. The spores can survive up to five months in the environment.<sup>2,3</sup> It can be transmitted from person-to-person, as well as by persons touching objects contaminated with the organism.<sup>3</sup> In the healthcare environment, *C. diff* has been cultured in rooms of infected individuals up to 40 days post discharge. Objects from which *C. diff* has been cultured include: scales, call buttons, telephones, floors, bedpans, toilets/commodes, bed frames, bathing tubs, and electronic thermometers.<sup>2-4</sup> It has also been cultured from healthcare workers' shoes, fingernails and fingertips, as well as the underside of rings.<sup>2,3</sup>

For the organism to cause disease, *C. diff* must be in the gastrointestinal system. Then, there must be a change in the normal colonic flora to allow the organism to grow and flourish. Finally, the *C. diff* must produce toxins.<sup>2</sup> The organism produces two toxins. Toxin A is an enterotoxin that causes excretion of large amounts of fluid from the bowel. Toxin B is cytotoxic, attacking and disintegrating cells of the intestines. In addition, *C. diff* produces tissue-degradative enzymes.<sup>3,5</sup> These processes elicit a profound inflammatory response within the colon that can result in a spectrum of diseases.

### Spectrum of Disease

At one end of the spectrum, *C. diff* can reside in the gut asymptotically.<sup>2,3</sup> Many patients colonized with *C. diff* do not develop clinical signs of the disease.<sup>6,7</sup> This organism can be isolated in up to 3% of healthy adults in the general population and from 50% to 80% of healthy newborns and infants.<sup>2,3</sup>

*C. diff* also causes simple antibiotic-associated diarrhea.<sup>2,3</sup> *C. diff* is a leading cause of nosocomial diarrhea in the US,<sup>8</sup> accounting for nearly 20% of antibiotic-associated diarrhea.<sup>9,10</sup> While there is evidence of community-acquired *C. diff*-related diarrhea, it is rare,<sup>2</sup> only about 20,000 cases are diagnosed in the outpatient setting annually.<sup>3</sup> The diarrhea is watery and may contain mucus.

More serious manifestations of infection are colitis and pseudomembranous colitis.<sup>2,3,6</sup> In addition to diarrhea, there may be loss of appetite, nausea, and abdominal tenderness or pain.<sup>3,7</sup> *C. diff* is responsible for 50-70% of antibiotic-related colitis.<sup>10</sup>

Approximately 1-3% of patients with *C. diff* infection develop fulminant colitis.<sup>11</sup> Symptoms include severe diarrhea, marked leukocytosis, high fever, chills, and severe lower quadrant or diffuse abdominal pain.<sup>11</sup> The colon may become so compromised that a paralytic ileus may develop,<sup>2</sup> in which case diarrhea is absent,<sup>2,11</sup> and constipation may be apparent.<sup>12,13</sup> Abdominal distension may develop.<sup>11</sup>

Toxic megacolon may ensue;<sup>11</sup> this is a life-threatening complication of colitis with an acute dilatation of all or a substantial portion of the colon to a diameter larger than 6 cm. It is associated with systemic toxicity.<sup>14</sup> Surgery is required in 65-71% of these cases.<sup>14</sup> The literature indicates that subtotal colectomy is the procedure of choice to reduce mortality.<sup>14</sup> Colonic perforation can occur,<sup>6,11</sup> and the protein-losing enteropathy can lead to hypoalbuminemia and ascites.<sup>2,11</sup>

Death is also a reported complication of *C. diff* infection.<sup>3,6</sup> Mortality associated with active *C. diff* infections is 0.6% for those with pseudomembranous colitis and 57% in patients requiring colectomy for toxic megacolon. The mortality rate for fulminant *C. diff* colitis is also high. This may be due to a failure to diagnose this disease in its early, more subtle stages, particularly if diarrhea is not present and abdominal findings are unclear.<sup>11</sup> Overall, studies have reported mortality rates associated with CDAD ranging from 0.6%<sup>9</sup> to 3%.<sup>1</sup>

### Concern

The incidence and severity of *C. diff* infection and related diseases appears to be increasing in developed countries, such as the US, UK, and Canada, probably due to increased use of broad-spectrum antibiotics, such as third-generation cephalosporins, during the past 20 years.<sup>6</sup>

A Canadian study describing cases of CDAD in one institution over a 13-year period found that incidence increased from 35.6 per 100,000 population in 1991 to 156.3 per 100,000 in 2003. In the patients aged 65 years or older, the rate increased from 102.0 to 866.5 during the same period. Complicated cases of *C. diff* infection increased from 7.1% to 18.2%. The proportion of patients who died within 30 days after diagnosis of *C. diff* infection increased from 4.7% to 13.8%.<sup>15</sup>

A study in the US Pacific Northwest describing a single institution's 20-year experience with *C. diff* colitis found that the number of cases rose by more than 30% when comparing the first and last 10-year periods. The mortality rate increased from 3.5% to 15.3%.<sup>16</sup>

## Clostridium Difficile: A Sometimes Fatal Complication of Antibiotic Use (Continued)

A study conducted in Pennsylvania indicated that incidence of fulminant *C. diff* colitis increased from 0% in 1990 to 3.2% in 2000.<sup>17</sup> Another study in a Pennsylvania teaching hospital<sup>18</sup> found an increase in the incidence of nosocomial *C. diff* from 2.7 to 6.8 cases per 1,000 discharges from 1999 to 2000-01. Further, 0.15 cases per 1,000 discharges of severe *C. diff*-related disease in 1999 rose to 0.60 in 2000-01. Some severe cases resulted in colectomy and death.

Recent case studies and anecdotal reports indicate that the course of *C. diff*-related disease may be changing. There appears to be a trend of more debilitating disease from this infection, higher mortality rates, and an increased need for operative treatment<sup>16</sup>—from an organism that has previously been considered relatively innocuous and responsive to treatment.<sup>17</sup>

### Risk Factors

Once *C. diff* becomes resident in the gastrointestinal tract, the predominant risk factor for developing disease is treatment with antibiotics, particularly broad-spectrum antibiotics.<sup>2,6-8,10,16,19</sup> Though disease may occur in the absence of a history of antibiotic therapy,<sup>2</sup> the use of the following antibiotics are most frequently associated with the development of *C. diff*-associated disease: cephalosporins, penicillins (ampicillin and amoxicillin), and clindamycin.<sup>3,7,16</sup> More recently, there have been reports of fluoroquinolone-associated CDAD,<sup>6,8,18</sup> including ciprofloxacin<sup>8</sup> and levofloxacin.<sup>18</sup> Antibiotic use, whether for prophylaxis or treatment, is a more important risk factor for *C. diff*-related disease and potentially poor outcomes than horizontal transmission via exposure to contaminated surfaces.<sup>16</sup>

Other general factors that determine whether *C. diff*-related disease develops include the type and timing of antibiotic exposure, the virulence of the strain of *C. diff*, and susceptibility or immune status of the patient.<sup>3</sup>

A multitude of patient factors may place patients at higher risk for *C. diff*-associated disease, increased mortality and morbidity, and recurrent infection. These include: advanced age;<sup>2,6-8,19</sup> severity of co-morbid conditions;<sup>2,19</sup> renal disease;<sup>2,6,12,13</sup> cancer;<sup>2</sup> diabetes mellitus;<sup>16</sup> diseases that compromise the immune system;<sup>7,16</sup> patients in intensive care units;<sup>2,19</sup> and patients with a low serum albumin.<sup>19</sup> In these situations, patients' ability to mount an immune response against the bacteria is compromised.<sup>8</sup>

Hospitalization is a risk factor. Studies indicate that from 13-31% of inpatients are colonized with *C. diff* if hospitalized more than one week, and 56% of these develop CDAD.<sup>1,3</sup> Those hospitalized more than four weeks may have a rate of acquisition of 50%.<sup>3</sup>

Gastrointestinal surgery is associated with increased risk of *C. diff*-associated disease. Procedures include: recent gastrointestinal (GI)/bowel surgery or manipulation of the GI tract;<sup>7</sup> non-surgical GI procedures;<sup>19</sup> presence of nasogastric tube/tube feedings.<sup>2,19</sup>

Patients with *C. diff* colitis and a markedly elevated leukocyte could have a poor prognosis and higher mortality rate than those without a leukemoid reaction.<sup>20</sup>

In the northern hemisphere during winter, CDAD outbreaks are more likely.

### Treatment

The following interventions can be implemented once a *C. diff*-associated disease is diagnosed:

- Discontinuing the offending antibiotic.<sup>2-4</sup>
- Administering another antibiotic only if continued antimicrobial therapy is needed and using antimicrobics that are less frequently associated with the *C. diff*-associated disease.<sup>3</sup>
- Providing supportive measures to correct fluid loss and electrolyte imbalances.<sup>3</sup>
- Implementing enteric isolation precautions for infected patients.<sup>3</sup>
- Treating the infection with vancomycin, metronidazole, or bacitracin as first line therapy.<sup>1-3</sup> Treatment is more likely to be successful if administered orally for 10 days.<sup>4</sup> However, use of vancomycin continues to be restricted because of the risk of developing vancomycin-resistant enterococcus. Ordinarily, oral vancomycin is reserved for patients with metronidazole intolerance. Metronidazole continues to be the drug of choice for CDAD.<sup>3</sup>
- If a patient receiving metronidazole therapy develops a white blood cell count greater than 20,000 cells/mm<sup>3</sup> and/or an elevated creatinine level, it may be an indication of more severe *C. diff*-related outcomes. Based on limited observational data, vancomycin treatment may be indicated in such cases.<sup>15,21,22</sup> Large, prospective, randomized controlled trials are needed, however, to confirm the effectiveness of such a change in ther-

## Clostridium Difficile: A Sometimes Fatal Complication of Antibiotic Use (Continued)

apy.

- In patients with refractory or recurrent *C. diff* colitis, a recently published uncontrolled study of 103 patients indicated that the rate of successful treatment was about the same whether prolonged metronidazole therapy or vancomycin was used.<sup>23</sup>
- Avoiding peristaltic agents<sup>3</sup> and antidiarrheal/antiperistaltic agents. Antidiarrheal agents such as loperamide may delay clearance of *C. diff* toxins from the patient's colon and may predispose the patient to toxic megacolon.<sup>4,7</sup>

Healthcare workers can provide supportive care; observe and document bowel habits and changes; document the characteristics of bowel movements; and educate patients/relatives about infection control procedures, such as handwashing and wearing of gloves and gowns if directly involved with the patient's incontinence care or toileting needs.<sup>2</sup> Several other approaches to the management and prevention of *C. diff* are being studied, as well, such as drugs (tinidazole or nitazoxanide), immunotherapy, vaccine, and probiotics (*Lactobacillus species* or *Saccharomyces boulardii*).<sup>1,4,23</sup>

### Prevention

Several interventions can help prevent *C. diff* transmission in the healthcare environment.

### Handwashing

The Centers for Disease Control and Prevention

(CDC) guidelines for hand hygiene in healthcare settings<sup>21</sup> contains information concerning: handwashing and hand antisepsis, hand hygiene technique, surgical hand antisepsis, selection of hand hygiene agents, and skin care. These guidelines include information that can be applied to preventing transmission of *C. diff* by healthcare workers. *C. diff* spores have been shown to be present on clinicians' hands, which may become contaminated through contact with infected fixtures, equipment, and patients and may then be instruments of contamination themselves.<sup>2</sup>

No agent used in antiseptic handwash or antiseptic hand-rub preparations is reliably sporicidal against *C. diff* (chlorhexidine, hexachlorophene, iodophors, alcohols, PCMX, triclosan). Spores may be physically removed from contaminated hand surfaces by washing hands vigorously with either non-antimicrobial or antimicrobial soap and water.<sup>21</sup>

While gloves are worn when caring for patients with *C. diff* diarrhea, after glove removal, hands are washed with a non-antimicrobial or an antimicrobial soap and water, or are disinfected with an alcohol-based hand rub. During outbreaks of *C. diff*-related infections, washing with soap and water after removing gloves is prudent, as frequent use of alcohol-based hand rubs may dry the skin, making it more vulnerable to breakdown.<sup>21</sup>

Handwashing also reduces contamination by the vegetative state of *C. diff*. Technique is important, however, if this decontamination process is to be ef-

### Emerging Strain of Clostridium Difficile

On April 11, 2005, at the annual meeting of the Society for Healthcare Epidemiology of America, infectious disease experts presented information concerning a new, highly toxic, strain of *Clostridium difficile*. This emerging strain is associated not only with severe diarrhea and colitis, but also colectomy and death.

The strain contains a mutation on a gene that regulates production of toxins A and B and which also may produce an additional toxin. The strain produces a higher level of toxin than most other strains, and it is also resistant to fluoroquinolones.

Since 2001, this strain has been identified in outbreaks in at least seven US hospitals in six states, as well as in Sherbrooke and Montreal in Quebec, Canada.

The hospital in Sherbrooke has substantially reduced the use of antibiotics known to be associated with *C. diff* infection. This was followed by a 33-50% reduction in *C. diff*-associated disease.

In May 2005, a Pennsylvania facility submitted a report to PA-PSRS indicating that the CDC had confirmed a genetically altered virulent strain of *C. diff* in a patient's specimen. A 30-year-old patient with multiple trauma received antibiotics, then developed a *C. diff* infection, which was treated with Flagyl. However, the patient developed pseudomembranous colitis and required an emergent total colectomy. Fortunately, the patient survived.

### Sources

Canadian Press. Quebec *C. difficile* strain has high toxin levels. [online]. 2005 Apr 11 [cited 2005 May 16]. Available from Internet: [http://www.ctv.ca/servlet/ArticleNews/story/CTVnews/1113222804128\\_6/?hub=Health](http://www.ctv.ca/servlet/ArticleNews/story/CTVnews/1113222804128_6/?hub=Health)

Acambis. Emerging strain of common bacteria *Clostridium difficile* is highly toxic. [online]. 2005 Apr 11 [cited 2005 May 16]. Available from Internet: [http://www.acambis.com/documents/sites/1/News\\_releases/SHEA\\_release.pdf](http://www.acambis.com/documents/sites/1/News_releases/SHEA_release.pdf)

International Society for Infectious Diseases. Researchers report emergence of epidemic strain of *C. difficile*. Archive number 20041004.2735. [online]. 2004 Oct 3 [cited 2005 May 16]. Available from Internet: [http://www.promedmail.org/pls/askus/f?p=2400:1001:491458::NO::F2400\\_P1001\\_BACK\\_PAGE,F2400\\_P1001\\_PUB\\_MAIL\\_ID:1000,26867](http://www.promedmail.org/pls/askus/f?p=2400:1001:491458::NO::F2400_P1001_BACK_PAGE,F2400_P1001_PUB_MAIL_ID:1000,26867)

## Clostridium Difficile: A Sometimes Fatal Complication of Antibiotic Use (Continued)

fective in preventing transmission. Such techniques are described in Figure 1.<sup>2,3,7,21</sup>

The Veterans Administration's National Center for Patient Safety has recently recommended that when *C. diff* is suspected, caregivers' hands hygiene includes increasing glove use to protect hands from contamination and handwashing with soap and water for decontamination.<sup>25</sup>

### Isolation

- Instituting contact and enteric precautions<sup>3,26</sup> until the patient has formed stools—ideally for 48 hours after diarrhea ceases.<sup>2</sup>
- Placing the patient in a private room with private toilet<sup>6,24</sup> or placing patients with *C. diff*-associated disease in the same room (cohorting).<sup>26</sup>
- Using disposable equipment and dedicating reusable equipment solely for that patient.<sup>7,26</sup>

### Personal Protective Equipment

- Wearing gloves when entering patients' rooms and when providing care to a patient with *C. diff*-associated disease.<sup>3,26</sup>
- Wearing gowns when there is a possibility that the clinician's clothing might become soiled while caring for the patient.<sup>7,26</sup>
- If the patient is experiencing explosive CDAD, using goggles might be prudent during incontinence care.

### Cleaning/Disinfection

Thorough cleaning of surfaces, equipment, reusable devices, and the hospital environment prevents *C. diff* transmission, acquisition, infection, and reinfection.<sup>7,26</sup> For example:

- After cleaning surfaces and reusable devices according to label instructions, using an EPA-registered hypochlorite-based disinfectant,<sup>3,6,24</sup> alkaline glutaraldehyde, or ethylene oxide.<sup>3</sup>
- Generic sources of hypochlorite, such as household chlorine bleach, may be diluted and used as labeled.<sup>26</sup>
- Cleaning with a hypochlorite disinfectant has been found to be more effective than using a neutral detergent to decrease the incidence of *C. diff* contamination.<sup>6</sup>
- Carefully cleaning/disinfecting environmental surfaces and items that are likely to be contaminated with fecal material and/or that are

When using soap and water:

- First, wet the hands with water
- Apply the manufacturer-recommended amount of the product to the hands
- Rub hands together vigorously at least 15 seconds
- Cover all fingers and surfaces of the hands
- Rinse hands thoroughly with water
- Dry completely with a disposable towel
- Turn off the faucet with the towel
- Avoid using hot water because repeated exposure to hot water may increase the risk of dermatitis

When decontaminating with an alcohol-based hand rub:

- Apply the product to the palm of one hand
- Rub hands together
- Cover all hand and finger surfaces until the hands are dry
- Follow the manufacturer's recommendations regarding the volume of the product to use

Figure 1. Handwashing Techniques

frequently touched.<sup>7,26</sup>

- Following manufacturer instructions for disinfection of endoscopes and other devices.<sup>26</sup>
- Alcohol-based disinfectants are not effective against *C. diff* and are therefore inappropriate for disinfection of environmental surfaces.<sup>26</sup>

### Prudent Antibiotic Use

Some healthcare facilities have changed antibiotic policies to limit use of broad spectrum antibiotics associated with *C. diff* infection.<sup>2</sup> The restriction of fluoroquinolone use among inpatients has been shown to decrease CDAD rates.<sup>8</sup> In one study, a formulary restriction of clindamycin was associated with a decrease in the incidence of CDAD.<sup>27</sup> Restricting the use of fluoroquinolones, however, needs to be balanced with the drug's advantages such as efficacy of oral administration and convenient dosing.<sup>8</sup>

Several hospitals in the UK have implemented antibiotic policies in which later-generation cephalosporins have been replaced with narrow-spectrum penicillins, fluoroquinolones, clarithromycin, piperacillin-tazobactam, metronidazole, trimethoprim, and/or aminoglycosides. Diseases treated were pneumonias, severe sepsis/septic shock, urinary tract infections, *H. influenzae*. The number of CDAD cases decreased significantly after the implementation of such policies.<sup>6,28,29</sup>

## Clostridium Difficile: A Sometimes Fatal Complication of Antibiotic Use (Continued)

### Education

An important factor in encouraging the prevention of *C. diff* transmission is education.<sup>8</sup> Healthcare workers can receive information about the disease, its epidemiology, methods of preventing transmission, hand-washing techniques, personal protective equipment, cleaning/disinfection, as well as the potential for severe sequelae from *C. diff* infection.

Healthcare workers can also teach patients, family members, and visitors about effective handwashing techniques, as well as use of personal protective equipment if family is to become involved in incontinence care/toileting of an infected patient.<sup>2,7</sup> The CDC has fact sheets for healthcare providers and the general public that describe the disease and how to prevent transmission.<sup>24,30</sup>

Both patients and healthcare workers also can develop awareness that if a patient with current or recent antibiotic use develops diarrhea or abdominal symptoms, it may be indicative of *C. diff*-associated disease with the potential for serious, life-threatening ramifications.<sup>11</sup>

While antibiotic use precedes almost all cases of *C. diff*-associated disease,<sup>11</sup> the onset of such diseases may occur during or several weeks after therapy.<sup>3</sup> *C. diff*-associated diseases are no longer exclusively hospital-acquired infections,<sup>2</sup> and symptoms do not necessarily begin during a hospital stay. Inpatient hospital stays continue to grow shorter, pre- and post-operative/procedure antibiotic therapy is conducted outside of the healthcare facility. The number of procedures conducted in ambulatory surgery centers continues to rise. Fluoroquinolones are prescribed for patients in the community because they can be taken orally.

All of these factors contribute to the likelihood of patients experiencing initial symptoms of *C. diff*-associated disease in a community setting. At least half of the *C. diff*-associated deaths reported to PA-PSRS indicated that the onset of diarrhea occurred outside the acute hospital setting.

Patients, family members, referring physicians, and healthcare workers in all settings can benefit from recognition that antibiotic use has the potential of causing substantial morbidity and even mortality. If the index of suspicion is raised about this link, medical intervention for evaluation and early treatment of *C. diff*-associated diseases may be sought in a more timely manner, thus helping to prevent serious negative outcomes.

### Notes

1. Kyne L, Hamel MB, Polavaram R, et al. Health care costs and mortality associated with nosocomial diarrhea due to *Clostridium difficile*. *CID* 2002 Feb 1;34:346-53.
2. Jenkins L. The prevention of *Clostridium difficile* associated diarrhea in hospital. *Nurs Times* 2004 Jun 29-Jul 6;100(26):56-7,59.
3. Hurley BW, Nguyen CC. The spectrum of pseudomembranous enterocolitis and antibiotic-associated diarrhea. *Arch Intern Med* 2002 Oct 28;162(19):2177-84.
4. Gerding DN, Johnson S, Peterson LR, et al. *Clostridium difficile*-associated diarrhea and colitis. *Infect Control Hosp Epidemiol* 1995;16:459-77.
5. Naaber P, Mikelsaar M. Interactions between Lactobacilli and antibiotic-associated diarrhea. *Advances in Applied Microbiology* 2004;54:231-60.
6. Riley TV. Nosocomial diarrhea due to *Clostridium difficile*. *Curr Opin Infect Dis* 2004 Aug;17(4):323-7.
7. McConnell EA. Prevent the spread of *Clostridium difficile*. *Nursing* 2002;32(8):24-5.
8. McCusker ME, Harris AD, Perencevich E, et al. Fluoroquinolone use and *Clostridium difficile*-associated diarrhea. *Emerging Infectious Diseases* [online]. 2003 Jun [cited 2004 Dec 15]. Available from Internet: <http://www.cdc.gov/ncidod/EID/vol9no6/02-0385.htm>.
9. Miller MA, Hyland M, Ofner-Agostini M, et al. Morbidity, mortality, and healthcare burden of nosocomial *Clostridium difficile*-associated diarrhea in Canadian hospitals. *Infect Control Hosp Epidemiol* 2002 Mar;23(3):137-40.
10. Koehler R, Mone M, Kimball E, et al. *Clostridium difficile* pericarditis complicating pseudomembranous colitis in a trauma patient. *J Trauma* 2003 Oct;55(4):771-3.
11. Longo WE, Mazuski JE, Virgo KS, et al. Outcome after colectomy for *Clostridium difficile* colitis. *Dis Colon Rectum* 2004 Oct;47(10):1620-6.
12. Kovithavongs T. *Clostridium difficile* colitis associated with chronic renal failure. *Nephrol Dial Transplant* 1999;14:2256-7.
13. Cunney RJ, Magee C, McNamara E, et al. *Clostridium difficile* colitis associated with chronic renal failure. *Nephrol Dial Transplant* 1998;13:2842-6. [Abstract]
14. Dobson G, Hickey C, Trinder J. *Clostridium difficile* colitis causing toxic megacolon, severe sepsis and multiple organ dysfunction syndrome. *Intensive Care Med* 2003;29:1030.
15. Pepin J, Valiquette L, Alary ME, et al. *Clostridium difficile*-associated diarrhea in a region of Quebec from 1991 to 2003: a changing pattern of disease severity. *CMAJ* 2004 Aug 31;171(5):466-72.
16. Morris AM, Jobe BA, Stoney M, et al. *Clostridium difficile* colitis. *Arch Surg* 2002 Oct;137:1096-100.
17. Dallal RM, Harbrecht BG, Boujoukas AJ, et al. Fulminant *Clostridium difficile*: an underappreciated and increasing cause of death and complications. *Ann Surg* 2002 Mar; 235(3):363-72.
18. Muto CA, Pokrywka M, Shutt K, et al. A large outbreak of *Clostridium difficile*-associated disease with an unexpected proportion of deaths and colectomies at a teaching hospital following increase fluoroquinolone use. *Infection Control and Hospital Epidemiology* 2005 Mar;26(3):273-80.
19. Eckel F, Huber W, Weiss W, et al. Recurrent pseudomembranous colitis as a cause of recurrent severe sepsis. *Z Gastroenterol* 2002 Apr;40(4):255-8.
20. Marinella MA, Burdette SD, Bedimo R, et al. Leukemoid reactions complicating colitis due to *Clostridium difficile*. *South Med*

## Clostridium Difficile: A Sometimes Fatal Complication of Antibiotic Use (Continued)

*J* 2004 Oct;97(10):959-63.

21. Gerding DN. Metronidazole for Clostridium difficile-associated disease: is it ok for mom? *Clin Infect Dis* 2005 Jun 1;40:1598-1600.

22. Pepin J, Alary M-E, Valiquette L, et al. Increasing risk of relapse after treatment of Clostridium difficile colitis in Quebec, Canada. *Clin Infect Dis* 2005 Jun 1;40:1591-7.

23. Musher DM, Aslam S, Logan S, et al. Relatively poor outcome after treatment of Clostridium difficile colitis with metronidazole. *Clin Infect Dis* 2005 Jun 1;40:1586-90.

24. Centers for Disease Control and Prevention (CDC). Guideline for hand hygiene in health-care settings. *MMWR* 2002 Oct 25;51 (RR-16):1-48.

25. Eldridge N, Danko L. Hand hygiene and diarrheal diseases in healthcare settings. *Topics in Patient Safety* 2005 May/Jun;5(3):2.

26. Centers for Disease Control and Prevention. Clostridium diffi-

cile: information for health care providers [online]. 2004 Sep 23 [cited 2005 Feb 3]. Available from Internet: <http://www.cdc.gov/ncdod/hip/gastro/ClostridiumDifficileHCP.htm>.

27. Climo MW, Israel DS, Wong ES, et al. Hospital-wide restriction of clindamycin: effect on the incidence of Clostridium difficile-associated diarrhea and cost. *Ann Int Med* 1998;128:989-95.

28. McNulty C, Logan M, Donald IP, et al. Successful control of Clostridium difficile infection in an elderly care unit through use of a restrictive antibiotic policy. *J Antimicrob Chemother* 1997 Nov;40 (5):707-11.

29. O'Connor KA, Kingston M, O'Donovan M, et al. Antibiotic prescribing policy and Clostridium difficile diarrhea. *QJM* 2004 Jul;97(7):423-9.

30. Centers for Disease Control and Prevention. Clostridium difficile: general information [online]. 2004 Aug 10 [cited 2005 Feb 3]. Available from Internet: <http://www.cdc.gov/ncidod/hip/gastro/ClostridiumDifficileGEN.htm>.



An Independent Agency of the Commonwealth of Pennsylvania

The Patient Safety Authority is an independent state agency created by Act 13 of 2002, the Medical Care Availability and Reduction of Error (“Mcare”) Act. Consistent with Act 13, ECRI, as contractor for the PA-PSRS program, is issuing this newsletter to advise medical facilities of immediate changes that can be instituted to reduce serious events and incidents. For more information about the PA-PSRS program or the Patient Safety Authority, see the Authority’s website at [www.psa.state.pa.us](http://www.psa.state.pa.us).



ECRI is an independent, nonprofit health services research agency dedicated to improving the safety, efficacy and cost-effectiveness of healthcare. ECRI’s focus is healthcare technology, healthcare risk and quality management and healthcare environmental management. ECRI provides information services and technical assistance to more than 5,000 hospitals, healthcare organizations, ministries of health, government and planning agencies, and other organizations worldwide.



The Institute for Safe Medication Practices (ISMP) is an independent, nonprofit organization dedicated solely to medication error prevention and safe medication use. ISMP provides recommendations for the safe use of medications to the healthcare community including healthcare professionals, government agencies, accrediting organizations, and consumers. ISMP’s efforts are built on a non-punitive approach and systems-based solutions.