

Empowering clinical decisions
in the fight against HAI*



Clostridium difficile
Associated Disease
From Diagnosis
to Outbreak Management

* Healthcare-Associated Infection

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Introduction

Clostridium difficile Associated Disease (CDAD) is currently defined as a nosocomial infection induced by antibiotic treatment. *Clostridium difficile* was identified as the cause of diarrhea and colitis in the late 1970s, and now accounts for 20 % of antibiotic-associated diarrhea cases.

Previously *C. difficile* was considered to be no more than a clinical nuisance, but since 2003 with strains causing more severe outbreaks and increased mortality in US and Canadian healthcare facilities, the *C. difficile* pattern has evolved for many to the “N°1 Superbug”. In August 2006, the US CDC considered the pathogen to behave in alarming new ways, with the emergence of deadly hyper-virulent strains and evidence suggesting the spread out of the hospital environment.

Increasing communication and information from National & International Health Organizations on measures for *C. difficile* detection and control, highlight the importance of this rising new health threat.

This document should provide basic information to understand CDAD, as well as its diagnosis, treatment and prevention in healthcare facilities. Available guidelines and case descriptions are also reported. Although not exhaustive, this booklet is intended as a succinct and practical reminder for laboratory professionals and clinicians.

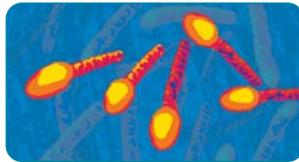
Clostridium difficile Associated Diseases (CDAD)

What is Clostridium difficile?

It is a naturally occurring, spore-forming, Gram-positive anaerobic bacillus and is widely found in soil and animals' intestines.

It is frequently present in the bowel of babies (up to 80%) but rarely in adults (<5%).

Spores confer the bacteria with resistance to heating, drying and a wide range of chemicals, including disinfectants.



How does C. difficile induce disease?

C. difficile flourishes in the human bowel when there is a **modification of the normal balance of bacterial intestine flora** (e.g. after antibiotic therapy).

Pathogenic strains of *C. difficile* produce two exotoxins.

- Enterotoxin A,
- Cytotoxin B.

They are responsible for the main symptoms and lead to diarrhoea through cytotoxic damages on the intestinal cells, an influence on gut neurons and an increase in the immune response.

An additional binary toxin (CDT) is also expressed in some virulent strain groups but its role in pathogenicity is not clear yet.

Do all strains of C. difficile induce disease?

Disease is mostly caused by **toxigenic strains** producing toxins A & B, or toxin B only. Groups or types of *C. difficile* not expressing toxins do not induce clinical illness.

But host interaction should also be taken into account as people can be colonized with toxigenic strains and remain asymptomatic.

What is the meaning of serogroups, ribotypes and toxinotypes?

In the 1980s, phenotypic methods were used to identify *C. difficile* strains, of which serogrouping is still considered to be a reference.

Initially, eleven serogroups (A-D, F-I, K, S, X) were identified, and now over 20 have been described which are well correlated to pathogenic and/or toxigenic characteristics.

Today, most attention is drawn toward genotypic methods based on chromosomal DNA. **No universal typing scheme currently exists** and strains are delineated depending on the method e.g. Restriction Endonuclease Activity (REA), Pulsed Field Gel Electrophoresis (PFGE), PCR ribotyping or Toxinotyping.

What are the main CDAD and their clinical signs?

The main CDAD that results from these infections ranges from mild upset to very severe disease. **Diarrhea is present in almost all patients** while the other symptoms are not systematically observed.

Main CDAD	CDAD Clinical Symptoms
<ul style="list-style-type: none">• pseudomembranous colitis (PMC)• toxic megacolon• perforations of the colon• sepsis• rarely death	<ul style="list-style-type: none">• watery diarrhea (at least three bowel movements per day for two or more days)• fever• loss of appetite• nausea• abdominal pain/tenderness• leukocytosis

How long after antibiotic therapy can CDAD occur?

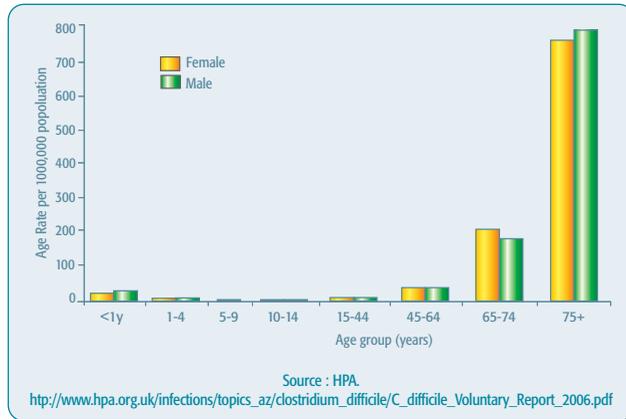
Symptoms can start a few days after the beginning of antibiotic therapy, and up to 8 weeks after its discontinuation (in 20% of cases).

What is the economical impact of CDAD?

In addition to enhanced patient morbidity and mortality, CDAD infections increase hospitalization costs (5-15,000 euros per case estimated in the UK and \$ 1.1 billion per year in the US) due to prolonged patient stay (8 to 21 days) and implementation of specific hygiene measures to contain an outbreak.

Who is at risk of getting CDAD?

People in good health are usually not infected by *C. difficile*. However, people requiring prolonged use of antibiotics, and the elderly are at greater risk of acquiring CDAD.



How frequent is CDAD?

Traditionally considered as a nosocomial infection, *C. difficile* accounts for 20% of the antibiotic-associated diarrhea cases with a rate of:

- 1/100 of patients undergoing antibiotic therapy in hospitals,
- 2/100,000 of patients undergoing antibiotic therapy outside hospitals.

Elderly and immunocompromised patients are at greater risk of CDAD

Does *C. difficile* touch other populations than those originally described?

Alarming, a 2006 Morbidity and Mortality Weekly Report (MMWR) indicated that there was an **increase in community-acquired CDAD in populations previously at low risk**. Half of them were 18 years old or younger, 40% of them had suffered a relapse and 25% had not recently taken antibiotics.

In a study of 1,233 patients from a British database, it was found that **heartburn drugs** and medication used to treat gastroesophageal reflux disease increased the risk of CDAD. **Proton pump inhibitors** and so-called **H2 receptor antagonists** increase this risk by three- and two-fold, respectively. **People taking NSAIDs** (non-steroidal inflammatory drugs) had also a 30% higher rate of *C. difficile* disease.

Which antibiotic treatment is associated with an increased risk of CDAD?

Historically, specific agents such as clindamycin, ampicillin, amoxicillin or cephalosporins were the most often associated with an increased risk of CDAD. But today, it is now admitted that **any antibiotic could be responsible for CDAD**.

How is the infection transmitted?

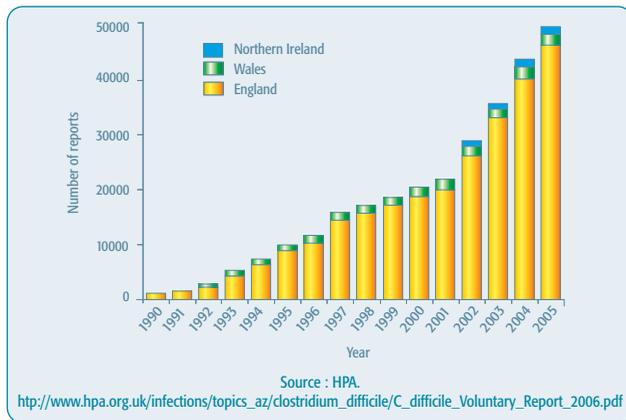
Infected patients excrete large amounts of bacteria/spores in their liquid feces. Therefore, spores can be disseminated to other patients through contact with:

- Infected patients,
- Healthcare staff,
- Contaminated surfaces and environment.

Beware of contact dissemination !

How has the incidence of CDAD evolved?

- In the US, data from the CDC reveal that hospitalisation with a discharge diagnosis of CDAD has significantly increased from 31/100,000 cases in 1996 to 61/100,000 in 2003.
- In the UK, the number of cases reported has dramatically increased since 2000. This is partly due to growing awareness, but there is also a real concurrent increase in the number of people developing *C. difficile* infections over the past 3 years.

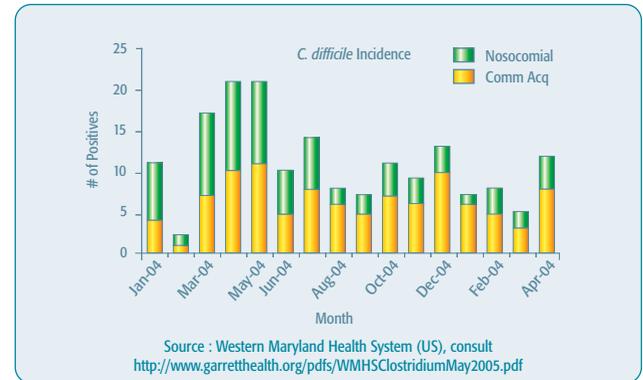


- On a European level, CDAD is severely underestimated due to lack of clinical awareness, lack of standardized strategies and surveillance.

Rocketing incidence is due to the emergence of both hyper-virulent strains and awareness

How has the incidence of CDAD evolved in the community?

The annual incidence of community-associated diseases was estimated at 7.6 cases per 100,000 outpatient antibiotic prescriptions in 2005 by the CDC.



In the UK, CDAD-diagnosed patients by general practitioners rose from less than 1 case per 100,000 in 1994 to 22 cases per 100,000 in 2004.

What are the possible reasons for changes in the disease epidemiology?

The increased rates and/or severity of disease may be caused by changes in antibiotic use, changes in infection control practices, or the emergence of a new strain of CDAD with increased virulence and/or antimicrobial resistance.

Strains Associated with Main *C. difficile* Outbreaks

Strains 027 and 017 are currently involved in the latest hospitals outbreaks

Clostridium difficile NAP1 / 027

Unusually severe outbreaks of CDAD associated with 7 to 22% mortality rate have been reported in several US and Canadian hospitals since 2003.

The most common strain isolated during these outbreaks was characterized as North America PFGE (NAP1), ribotype 027, and toxinotype III.

1 What are the main features of NAP1/027?

- Resistance to fluoroquinolones and cephalosporin,
- Production of binary toxin CDT (role not yet clarified) in addition to toxins A&B,
- Association with more severe types of the disease requiring more colectomies,
- Higher sporulation levels than other strains.

2 Does fluoroquinolone resistance affect management of the NAP1/027 strain?

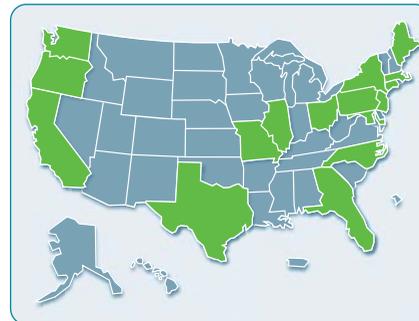
Increased fluoroquinolone resistance does not affect the management of infections caused by this strain. Fluoroquinolones have never been recommended for treatment of *C. difficile*-associated disease and susceptibility testing is performed only as a part of an epidemiological investigation. However, resistance to fluoroquinolones may provide the new strain with an advantage over susceptible strains to spread within healthcare facilities where these antibiotics are commonly used.

3 What is the NAP1/027 antibiotic susceptibility pattern?

Antibiotic	Susceptibility Pattern	MIC
Erythromycin	Resistant	>256 mg/l
Ciprofloxacin	Resistant	>32 mg/l
Clindamycin	Susceptible	=4-6 mg/l

4 What are the main areas affected by NAP1/027 outbreaks?

This strain is still disseminating in the US as reported by the CDC in 2006. As of 2003, it was identified as being the cause of outbreaks in the UK, Netherlands, Belgium and more recently in June 2006 in the North of France.



→ States with the North American Pulsed Field Type 1 strain of *C. difficile* confirmed by CDC as of May 15, 2006 (N=17)

Clostridium difficile 017

Severe outbreaks due to toxin A negative, toxin B positive (A-, B+) strains have been reported since 1999. PCR ribotype 017 toxinotype VIII has been shown to be the strain (A-, B+) most frequently found in clinical isolates of various geographical areas. Genetic **Clindamycin resistance** identified through the presence of the erm(B) gene is a common feature found in 017 strains which present a **worldwide clonal spread**.

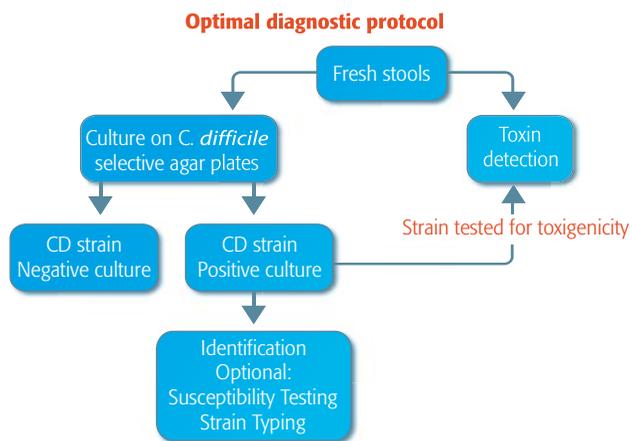
CDAD Diagnosis and Identification

As revealed by a European survey conducted in 2002, marked differences exist between laboratories concerning the methods and strategies used for diagnosing CDAD. They depend on the regional incidence rates and local laboratory capacities/abilities.

If toxin detection is universally implemented, routine use of culture varies considerably from country to country and even within a same country.

As National Guidelines are available only in a few countries, this section will describe the main techniques associated with the **key encountered strategies** and existing recommendations:

- CDAD diagnosis based on toxin A / B detection only (UK and US),
- CDAD diagnosis based on parallel toxin A/B detection and *C. difficile* culture as recommended by the ESGCD (European Study Group on *Clostridium difficile*).



What are the criteria for CDAD testing?

In most cases (58%), CDAD investigations are carried out on request by the physician. The **main clinical criterion** for requesting a CDAD laboratory diagnosis is **symptomatic disease**. Therefore, patients suffering from diarrhea and/or abdominal pain (except in cases of suspected ileus) should be tested in the following situations:

- Nosocomial infection,
- Patients having taken antibiotics within the past 30 days (sometimes extended up to the past 8 weeks),
- Patients belonging to high risk groups (i.e. over 65 years of age, immuno-compromised, severe underlying disease) regardless of whether they are in the community or hospital.

- Any diarrhea lasting more than 3 days without another known pathogen (with or without previous antibiotic therapy; community acquired).

In the Netherlands, testing all fecal diarrheic specimens from patients hospitalized for more than 3 days results in a 20% increase of the number of CDAD-diagnosed patients.

What is the correct laboratory sample type required for diagnosis?

- Fresh stools, **within one or two hours** of passage,
- Watery, unformed or loose stool (no rectal swabs),
- One (two maximum) specimen from a patient at the onset of a symptomatic episode,
- Submitted in a clean watertight container,
- No transport media are needed.

Samples are processed for toxin detection as soon as possible, or stored either at 2-8°C for 3 days maximum or at -80°C. The toxin degrades at room temperature and may become undetectable within 2 hours after collection of a stool specimen.

Storage at room temperature or at -20°C alters toxin content.

What are the different toxin detection techniques?

1 Cytotoxicity activity (CTA)

Detection of toxin activity in stools from patients suffering from antibiotic-associated colitis has led to the discovery of *C. difficile* as the main causative agent for this infection.

Therefore, cell cytotoxicity remains the gold standard to which most EIA methods are compared. However, method sensitivity depends on the cell line and the dilution titer used for the detection of a positive result.

CDAD Diagnosis and Identification

The main drawbacks of this technique are :

- Its labour intensity,
- Lack of standardization,
- Poor time to result,
- Need for cell culture,
- Need for trained technician to read results.

2 Enzyme Immunoassay (EIA)

EIA commercial kits offer a rapid and easy-to-use alternative technique to cell cytotoxicity. Results are obtained within 2 hours. Toxins are detected using monoclonal antibodies coated on a support (solid for conventional Immunoassay and membrane for an immunochromatographic test). Now, toxin A&B detection is included as recommended by the existing guidelines.

3 Molecular techniques

Previously limited by the presence of Taq-polymerase inhibitors in stools, the improvement of extraction techniques now enables the development of real-time PCR methods based on toxin A and/or B gene detection. Currently, the use of molecular techniques to detect *C. difficile* infections remains limited and is not yet implemented in routine diagnostic use.

Why should I consider culture for CDAD diagnosis?

Culture is the most sensitive method and is essential for:

- Investigating patients with severe/complicated disease,
- Suspected cases with negative stool results,
- Epidemiological studies in case of outbreaks,
- Antibiotic susceptibility testing.

Consequently, culture along with cytotoxin detection, should still be considered as essential in the laboratory diagnosis of CDAD.

1 How can I culture efficiently and recognize *C. difficile* colonies?

Culture of *C. difficile* is performed during 24 - 48hrs on a selective medium (Cycloserine-Cefoxitin-Fructose Agar [CCFA]) in an anaerobic environment at 37°C.

Specific agar plates supplemented with blood are also used for highly selective culture of *Clostridium difficile*.

With experience, presumptive identification of *C. difficile* is performed by:

- Visual inspection of bacterial colonies that demonstrate typical morphology on agar,
- Identifying a horse-dung smell,
- Yellow-green fluorescence under UV light (360nm),
- Positive-Gram staining.



Clostridium difficile agar plate

2 How can I identify *C. difficile* with confidence?

Culture isolates, which cannot be identified using the above means, should be biochemically tested through specific identification strips.



Example: API® 20A and rapid ID 32 A

3 What is the use of alcohol shock procedure?

An alcohol shock procedure (a mixture of stool and methylated spirit (1/1) vortexed and settled at room temperature for 30 min) can be used to select bacterial spores prior to culture, especially if using non-selective media.

4 What is toxigenic culture and its interest in CDAD diagnosis?

Toxigenic culture associates culture on selective CCFA and toxin detection of the isolated strains using CTA or EIA technique. This method has no rapid diagnostic value but can be useful in cases where patients have negative toxin stool results, but present clinical symptoms of an ongoing infection.

Around 10% of CDAD patients are additionally diagnosed using toxigenic culture.

CDAD Diagnosis and Identification

Should *C. difficile* be tested for antibiotic susceptibility?

Apart from epidemiological investigation, routine susceptibility testing is seldom performed on *C. difficile* as most CDAD respond to metronidazole or vancomycin treatment.

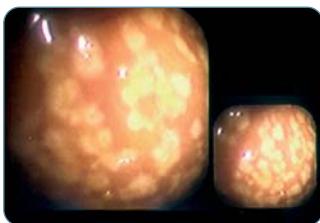
However, recently isolation of metronidazole- and vancomycin-resistant strains in Spain, and a metronidazole-resistant 027 isolate in Austria from a UK tourist, showed that surveillance of the antibiotic susceptibility of *C. difficile* may be worth considering at least on a national level. In addition, easy- and ready-to-use antibiotic susceptibility tests are now available in strip or microtiter plate format.

Antibiotic susceptibility of *C. difficile* may be worth considering !

What additional information can be obtained from other diagnostic methods ?

1 Endoscopy

It is used mainly to confirm the extreme manifestation of CDAD (pseudomembranous colitis [PMC]). Most authorities consider this technique to be subsidiary, i.e. when clinical suspicion has not been confirmed by less invasive techniques.



Pseudomembranous colitis, endoscopy[©]
BSIP, Cavallini James

2 Fecal leukocytes and lactoferrin

Detection of fecal leukocytes through methylene blue staining, can help distinguish between inflammatory and non-inflammatory causes of diarrhea. The analysis should be performed rapidly after specimen collection to prevent leukocyte degradation. If rapid analysis is not possible, lactoferrin, as a stable validated marker of fecal leukocytes, can be an alternative to direct leukocyte staining.

Which are the advantages/drawbacks of the main strain classification methods?

1 Serogrouping

Mainly used for epidemiological purposes, serogrouping was one of the early methods developed in 1985 to distinguish between strains, which may have specific pathogenicity.

2 Molecular Identification Techniques

PFGE enables the separation of large DNA fragments and is very discriminatory due to the use of specific-cutting restriction endonucleases. It has been used mainly to investigate outbreaks in the US. Its drawbacks are the high equipment cost, as well as its slowness, complexity and inability to type some serogroup G strains.

PCR ribotyping offers considerable advantages in terms of rapidity, reproducibility and technical ease. It is only marginally less discriminant than PFGE. It is based on comparison patterns of PCR products of the 16S-23S rRNA intergenic spacer region, and up to 170 different ribotypes have been isolated so far by the Anaerobe Reference Laboratory in Cardiff, UK.

Toxinotyping offers partial correlation with serogrouping and good correlation with other molecular typing techniques. Toxinotyping is based on PCR-RFLP analysis of a 19kb region encompassing the *C. difficile* pathogenicity locus; it can enable the follow-up of emerging new variants of toxin-producing genes. More than twenty toxinotypes (I-XX) have currently been described.

Method	Culture	Immunoassay	Cytotoxicity	PCR
For	Strain isolation Susceptibility testing	Toxin A&B detection Diagnosis	Toxin B detection Diagnosis	Toxin B gene detection Typing
Time	1-4 days	15 min to 2 hrs	1-2 days	> 2 hrs
Easiness	++	+++	---	--
Main features	Manual Sensitive Low price	Standardized Automated Rapid	Gold standard Not standardized Tedious	Epidemiology Not cost competitive

Protocols for the treatment of *C. difficile* infections are well defined. However, the management of relapse patients remains an issue.

What should be the first reaction?

In 15 - 23% of patients with symptomatic CDAD, **stopping the offending antibiotic therapy** will resolve the diarrhea within 2-3 days, without additional treatment.

Who should receive treatment?

Treatment has to be prescribed in cases of:

- Severe or persisting symptoms,
- Elderly or fragile patients,
- Ongoing antibiotic therapy that cannot be stopped.

What is the treatment of choice?

The mainstay of treatment remains **metronidazole** (MIC: 0.125-1 mg/l) administered orally with an appropriate course of 10 days. For those who cannot tolerate oral administration, an intravenous route can be used at appropriate levels. This antibiotic is usually the preferred treatment for initial episodes of CDAD in order to limit the vancomycin selection of glycopeptide-resistant enterococci. Metronidazole is also far less expensive than vancomycin.

Oral vancomycin (MIC: 0.25-4 mg/l) is usually used in second intention when patients do not respond to/tolerate metronidazole treatment, but it can be used as a first-line treatment in cases where patients:

- Have severe life-threatening disease,
- Are pregnant,
- Are <10 years old.

An intravenous route is not recommended, but administration via enteral tubes has been reported successful if required.

Are there alternatives to treatment with metronidazole or vancomycin in CDAD?

A high molecular weight toxin-binding polymer (Tolevamer) has been shown to be as efficient as vancomycin in a phase II study (August 2006).

A nitrothiazolide (nitazoxanide), which blocks the anaerobic metabolism of eukaryotes' and is usually used for parasitic infection, was judged similar to vancomycin.

How to assess the patient's clinical recovery?

Once clinical symptoms have ceased, there is usually no need to perform further diagnostic tests to assess patient recovery. In some facilities, patient isolation is discontinued after 2 or 3 toxin negative sample results. In Quebec (Canada), patient isolation is prolonged for 72 hrs after symptoms have ceased.

Up to 40% of patients remain carriers of *C. difficile* after treatment.

How to define and manage recurrent CDAD?

Recurrent CDAD is:

- Observed in 10 - 20% of the cases (except in the last CDC epidemiological bulletin, where 40% of recurrences are linked to the emergence of a hyper-virulent strain),
- Considered as being an "early recurrence" when occurring within 1 to 3 weeks after successful treatment,
- Considered as being a "late recurrence" when occurring several months after successful treatment.

Diagnosis and treatment of CDAD recurrences are performed **in the same way as the initial episode** and is efficient in 90% of the cases. However, patients can go on presenting multiple recurrences.

For those patients who experience more than two CDAD recurrent episodes, a number of **empiric strategies** may be used but no consensus exists yet. They are aimed at getting rid of the bacterial vegetative form, as well as restoring the normal intestinal flora. Therefore, standard, prolonged or "pulse" antibiotic therapy can be combined with probiotic compounds such as *Saccharomyces boulardii* or *Lactobacillus rhamnosus* GG.

Outbreak Prevention and Control

Prevention and control of CDAD outbreaks in hospitals are based on both:

- The correct use of antibiotics,
- Compliance with infection control measures.

Correct use of antibiotics ensures that the bacteria does not become resistant, and exposure of other patients' to the organism is limited by implementing infection control measures such as:

- Early recognition and diagnosis of the disease,
- Patient isolation and prompt treatment,
- Alert mechanism in place in the healthcare facility,
- Adequate hygiene/infection control.

How to manage CDAD patients?

Patients diagnosed as having CDAD should be treated and isolated from the rest of the hospitalized patients.

Room placement could be managed as follows:

- Private rooms would be recommended for residents who are fecally incontinent or cannot practice good hand washing,
- Cohort symptomatic CDAD residents only with other symptomatic CDAD residents.

The patient should also be instructed on optimum toilet hygiene such as good hand hygiene, and flushing toilet with the lid closed (to avoid aerosol release).

How to manage the spread of contamination in the environment?

Contamination of the environment and healthcare workers' hands are usually closely related. Therefore, implementing infection control measures (see below) is recommended to be able to contain the spread of the bacteria.

① Barrier Methods

Contact precautions should be used for CDAD patients:

- Gloves should be used when entering the room and specifically when handling body substances,
- Gowns should be worn in case of physical contact with the patient,
- Common use instruments, such as thermometer, stethoscopes, must be patient-specific and not shared with other patients,
- Hands should be washed frequently, preferably with soap and water, as alcohol-based hand rubs are not effective against spore-forming bacteria.



Spores are highly resistant and can last for several weeks in the environment

② Environmental Cleaning

- Disinfection with hypochlorite-based solution (500-1600ppm available chlorine) is effective in reducing the number of *C. difficile* positive cultures from environmental surfaces (21% to 98%, respectively).
- Resident environment cleaning should be performed thoroughly at least twice a day, and special attention given to items such as bedrails, bedside commodes, toilets, and floors which are likely to be contaminated with feces or spores.
- Disinfection of endoscopes should be performed according to the manufacturer's instructions.
- Hydrogen vapours were also demonstrated as being efficient in *C. difficile* room decontamination.

Cleaning agents shall be carefully chosen as some disinfectants could enhance strains' sporulation capabilities.



**Correct handwashing
is essential**

How to better manage hygiene rule compliance?

Implementing some simple actions can help increase healthcare workers' adherence to hygiene rules, such as:

- Easy access to hand washing material (such as providing bedside or pocket size bottles of hand-rub),
- Use of cleaning agents that protect rather than irritate skin,
- Hospital-wide educational programs (including cleaning staff as well as nurses and physicians),
- Posters as a reminder of basic rules,
- Personal discussion with an infectious disease physician (more effective than e-mails).

**Education and
easy access to cleaning
agents for better hygiene
management**

Why establish restriction of antibiotic use?

Restriction of antibiotic use has been demonstrated successful in reducing the rate of CDAD in numerous examples implying broad-spectrum antibiotics, such as cephalosporins, clindamycin or various others. A successful restrictive antibiotic policy should then be based on:

- Antibiotic prescription guidelines with validated effectiveness,
- Education and awareness of the risks of CDAD following the use of a specific class of antibiotic,
- Monitoring antibiotic use and implementing automatic stop dates on antibiotic prescriptions.

Surveillance of antibiotic use can be settled either at patient level or at population level using the Anatomical Therapeutic Chemical/ Define Daily Dose (ATC/DDD) system.

**Reducing the use
of antibiotics means less CDAD
and less resistant
strains**

What are the basics for establishing worldwide CDAD surveillance?

Case reports of CDAD as well as reporting outbreaks are two cornerstones for better assessment and monitoring of the disease burden.

A common CDAD case definition should also be shared by different countries and was recently proposed by the ESGCD based on the published experience in the US and Canada (see chapter on Official Guidelines).

Clostridium difficile Official Guidelines

● International Code for CDAD

In the International Classification of Diseases, 9th Revision, Clinical Modification organisation (i.e. NHDS) to determine the number of discharged diagnoses

(ICD-9-CM), code (008.45) CDAD is specific for "intestinal infection introduced in 1993 and is used by National Hospital Discharge Survey within a country (i.e. the US).

Country	Recommended National Guidelines published by	Year	National Surveillance of CDAD / or Disease Notification	Reference or Websites
US	Society for Healthcare Epidemiology of America (SHEA)*	2002	<i>C. difficile</i> infection is not a reportable disease in most US states.	Simor et al., Infect. Control Hosp. Epidemiol. 23 (2002) 696-703 http://www.shea-online.org
	CDC fact sheets	2006		http://www.cdc.gov/ncidod/dhqp/id_CdiffFAQ_general.html
Canada	Public Health Agency of Canada	2005		http://www.phac-aspc.gc.ca/c-difficile/index.html
Quebec	Institut National de Santé publique du Québec		Only Quebec and Manitoba (Canada) require CDAD case reporting.	http://www.inspq.qc.ca/pdf/publications/362-Cdifficile-LignesDirectrices-3eEdition.pdf
Europe	European Centre for Disease Prevention and Control [ECDC]**		Surveillance program implementation is under the responsibility of each country.	http://www.ecdc.eu.int
	European Study Group on <i>Clostridium difficile</i> (ESGCD)	2006		http://www.escmid.org/sites/index_f.aspx?par=2.5
Belgium	Belgium Infection Control Society	2006	National surveillance program introduced from June 2006.	http://www.belgianinfectioncontrol society.be
France	Institut National de Veille Sanitaire	2006	Surveillance introduced in 2007.	www.invs.sante.fr/raisin
Germany	Robert Koch Institute	2006		http://www.rki.de
Ireland	Communicable disease surveillance Centre Northern Ireland	2006	Mandatory surveillance since 2005.	http://www.cdscni.org.uk/publications/AnnualReports/pdf/HCAI2005Version3.pdf
Netherlands	Center for Infectious disease Control at the National Institute for Public Health and the Environment (RIVM)	2005	National surveillance program introduced from September 2005	
	- Working Party on Infection Prevention	2006	"Infection prevention measures for <i>Clostridium difficile</i> ".	www.wip.nl
UK	National <i>Clostridium difficile</i> Standard Group	2004	Mandatory case reporting since 2004. Screening all patients > 65 years old from community and hospital with diarrhea.	http://www.hpa.org.uk

CDAD Case Definition

● Case definitions for CDAD from the European Society of Clinical Microbiology and Infectious Disease (ESGCD)

CDAD Case

Criterion 1:

- diarrheal stools or toxic megacolon, AND
- a positive assay for *C. difficile* toxin (either an immunoassay detecting toxin A or B, or a neutralised cell cytotoxicity assay), OR a positive stool culture with a toxigenic strain.

Criterion 2:

pseudomembranous colitis observed on lower gastrointestinal endoscopy.

Criterion 3:

colonic histopathology characteristic of *C. difficile* infection (with or without diarrhea), on a specimen obtained during endoscopy, colectomy or autopsy.

CDAD Recurrence

Two episodes of CDAD in the same patient are considered to be distinct events if they occur >2 months apart.

An episode that occurs within 2 months of a prior episode (i.e., there is a return of symptoms less than 2 months after the end of the treatment) is considered to be a recurrence of the initial disease.

A recurrence can correspond either to a relapse with the same strain or re-infection with a different strain. It is not possible in clinical practice to differentiate between these two mechanisms, and the term "recurrence" is used as a designation for both.

CDAD Severe Case and Graduation

A severe case of CDAD can be defined as a patient who:

- admitted to an ICU for CDAD (e.g. for shock requiring vasopressor therapy);
- OR underwent surgery (colectomy) for megacolon, perforation or refractory colitis;
- OR is readmitted for CDAD;
- OR died within 30 days after CDAD diagnosis, if the death can be associated with CDAD, i.e.;
- CDAD is the primary (attributable) cause of death,
- OR CDAD is a contributory cause of death.

The severity of CDAD can also be graded:

Criteria	Mild	Moderate	Severe
Fever	None	37.5°C – 38.5°C	≥38.6°C
Leukocytosis	None	15 – 19 x 10 ⁶ /l	≥20 x 10 ⁶ /l
Abdominal symptoms	None	Severe abdominal pain	Symptoms of peritonitis
Complication	None	Lower digestive hemorrhage (with stable blood pressures)	- Lower gastro-intestinal hemorrhage (with unstable blood pressures) - Perforation of the colon - Sepsis due to colitis - Renal dysfunction

CDAD Origin

Healthcare-associated, nosocomial:

- CDAD in patients with onset of symptoms occurring at least 72 hours after admission, or within 4 weeks after discharge.

Healthcare-associated, imported from another institution:

- CDAD in hospitalized patients within 72 hours after admission or in outpatients,
- AND a history of hospitalization or ambulatory care (dialysis, ambulatory surgery, ambulatory medical care, intravenous therapy) in the previous 4 weeks.

Community-acquired :

- CDAD in outpatients or in hospitalized patients within 72 hours after admission,
- AND no history of hospitalization or ambulatory care in the preceding 4 weeks;

Unknown: cases that cannot match the above definitions.



C. difficile: What Matters Tomorrow?

- **Establishing close surveillance and appropriate classification of CDAD cases will surely help answer/confirm some of the concerns below.**

Can *C. difficile* spread into the community?

Having already penetrated the Quebec communities, there is evidence suggesting the spread of *C. difficile* out of US hospitals. Surveillance in the Netherlands revealed a high incidence rate (36%) of community CDAD diagnosed patients, but 1/3 patients had been hospitalized within the months previous to disease onset.

CDAD has already spread into the community in Quebec and evidence also indicates possibly in the US

Is transmission through food possible?

A 1998 study by J. Brazier demonstrated the ubiquitous presence of *C. difficile* in the environment (soil: 21%, untreated water: 47-87%, swimming pools: 50% and pets: 7%) but the carriage in animals in the human food chain was found to be rather low (ranging from 0 to 1.6%) and also for raw vegetables (2.2%). More recently, **screening for the bacterium in meat** bought in Arizona (US) grocery stores gave a **25% rate of positive results!** The same results were obtained in Ontario and Quebec (Canada). The concern is that **spores are known to survive the cooking process**, but transmission between people and animals still has to be demonstrated.

Is pet to human transmission possible?

Animal reservoirs have been recognized in several studies. In June 2006, a publication appeared for the case of the 027 variant *C. difficile* strain isolated from a healthy 4-year-old toy poodle that visits people in hospitals and long-term care facilities in Ontario (Canada). The number of CDAD cases increased in the facility around the time the dog's fecal specimen was collected. **This canine isolate was found indistinguishable from the major strain implicated in outbreaks** of highly virulent CDAD around the world, leading to the hypothesis that CDAD can also manifest as a zoonotic disease.

The role of animals should be considered in future studies to evaluate the dissemination of this strain and investigate the movement of *C. difficile* into the community.

Can we prevent CDAD by vaccination?

The host immune response (IgA & IgG) plays a fundamental role that can explain the large disparities in the clinical manifestation of CDAD. Increased antibody concentrations have been correlated with favourable outcome. The presence of antibodies directed against toxins are protective for the patient and may also prevent relapse. Therefore, patients suffering from a deficient immune response could benefit in the future from treatment through parenteral administration of concentrated anti-toxin immunoglobulins, or prevention through vaccination. These two approaches are currently in the first stages of clinical evaluation.

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bioMérieux Global Solution for *C. difficile*

Complete Solution for <i>C. difficile</i>	Product Name	Reference
Toxin Detection	VIDAS® <i>C. difficile</i> Toxin A&B	30118
Culture plates	Clostridium difficile Agar	43431 ¹
Identification	API® 20 A & rapid ID 32 A	20300/32300
Susceptibility Testing	ATB™ ANA ² /ATB ANAEROBIE ³	14269 ¹ /14001 ¹
Molecular Typing	DL <i>Clostridium difficile</i>	270609

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³ CASFM Standard