

PANDEMIC INFLUENZA

Background

During the last century, there were three influenza pandemics, each caused by a novel type A influenza virus of avian origin. In the 1957 and 1968 outbreaks, the responsible viruses, with components of previous human and avian viruses, emerged after viral reassortment occurred in a common host (i.e. porcine). The highly pathogenic virus of 1918 likely emerged after mutation of genetic elements from what had originally been a purely avian pathogen.

In general, influenza pandemics arise when all four of the following occur:

- A novel influenza A virus emerges as a result of an antigenic shift
- There is efficient human-to-human viral transmission
- The new virus is associated with serious morbidity and mortality
- The population has little or no immunity to the virus

Recent outbreaks of avian influenza in Asia and other parts of the world have been of great concern. Such widespread dissemination of these avian influenza viruses is unprecedented, and, in some instances, these viruses have been shown to spread from chickens directly to humans. Of even more concern are the reports of transmission, albeit inefficient, of potentially lethal infections amongst humans.^{1,2}

The Ontario Ministry of Health has recommended that physicians be alert for any persons presenting with severe influenza-like illnesses (ILI) who have a history of travel to avian influenza-affected areas

(currently Thailand, China, Cambodia, Vietnam, the Democratic People's Republic of Korea). Physicians are to report severe ILI cases to the local medical officer of health and to collect clinical samples from these patients for viral culture as soon as possible.³ Public health officials from around the world have reminded the public that the next pandemic is long overdue.



Projections

It is estimated that an influenza pandemic in Ontario, depending on the number of people infected, could result in between 22,000 and 52,000 hospitalizations, 5,000 to 12,000 deaths and 980,000 to 2.25 million outpatient visits. It is expected that the pandemic will last much longer than most other emergency events, and may include waves of influenza activity separated by months. The numbers of health-care workers and first responders available to work will be significantly reduced. Pandemic influenza will have an impact far beyond the health sector, and provincial planning to address the broader issues is ongoing.

Antiviral Medications/Vaccinations

Four influenza antiviral medications (amantadine, rimantadine, oseltamivir, and zanamivir) are approved for the treatment and/or prevention of influenza. However, the influenza A (H5N1) viruses identified in human patients in Asia in 2004 and 2005 were resistant to amantadine and rimantadine. This fact, and the side effect profile and need for individual dosing of amantadine have resulted in the widespread agreement to focus on oseltamivir as the drug of choice in a pandemic situation.

Monitoring of avian viruses for resistance to influenza antiviral medications is ongoing. A vaccine would probably not be available during the first wave of a pandemic, as once the pandemic strain is identified, it will take 3 to 4 months before a vaccine will be widely

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available. Pandemic Influenza plans have focused on the acquisition and distribution strategies of antivirals and vaccines as well as the establishment of priority groups to be immunized and to receive antiviral medication. Canada's contract with its domestic manufacturer calls for the manufacture of 8 million doses a month over a 4-month period, in the event of an influenza pandemic. ■

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1. Monto, A.S. NEJM 2005; 352(4): 323-325.
2. Ungchusak, K. *et al.* NEJM 2005; 352(4): 333-340.
www.health.gov.on.ca/english/providers/program/emu/emu_mn.html
3. http://www.health.gov.on.ca/english/public/pub/ministry_reports/pandemic/pandemic_rep04.pdf

Additional information is available at:

Public Health agency of Canada: www.phac-aspc.gc.ca/tmp-pmv/index.html

Ministry of Health and Long-term Care:

http://www.health.gov.on.ca/english/providers/program/emu/emu_mn.html

MOHLTC 24/7 Healthcare Provider Hotline: 1-866-212-2272

CLOSTRIDIUM DIFFICILE - associated diarrhea

OVERVIEW

Clostridium difficile is a common cause of antibiotic associated diarrhea in inpatient and outpatient populations. In the recent past, Canadian institutions have reported an increase in the incidence, recurrence and case fatality rates of *C difficile*-associated disease (CDAD)^{1,2}. The organism produces spores that can survive for long periods in the environment thus facilitating nosocomial outbreaks. The hospital clone described by Pepin *et al* produces a binary toxin, has a *tedC* gene deletion and is resistant to newer fluoroquinolones, all traits that may contribute to its increased incidence and virulence². The organism is spread by the fecal-oral route.



Figure 1. Gram stain of *C. difficile* showing gram-positive bacilli with subterminal spores. Courtesy of Dr. Kenneth Todar, University of Wisconsin-Madison

CLINICAL FEATURES

More than 50% of healthy neonates and infants are asymptomatic carriers of *C difficile*, compared to 0%-3% of healthy adults. Colitis can be complicated by toxic megacolon, colonic perforation, sepsis

and death. CDAD may initially present with leukocytosis and fever, even in the absence of diarrhea. Symptoms may arise within one day of commencing to 10 weeks after cessation of antibiotic treatment. Risk factors for CDAD include antibiotic exposure (especially third-generation cephalosporins, fluoroquinolones and clindamycin), antineoplastic agents, advanced age and presence of underlying comorbidities.

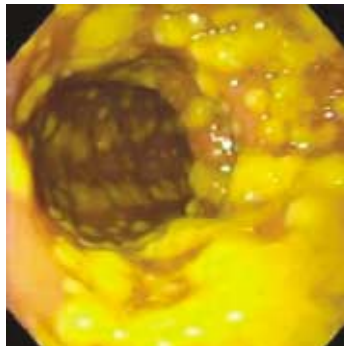


Figure 2. Pseudomembranous colitis. Courtesy of Gregory G. Ginsberg, MD, University of Pennsylvania.

LABORATORY DIAGNOSIS

The laboratory diagnosis of CDAD most often consists of enzyme immunoassays (EIA) for the detection of *C. difficile* toxins A and B. Most outpatient stool specimens submitted to MDS for the diagnosis of CDAD are forwarded to Ministry of Ontario Public Health Laboratories for EIA testing. The sensitivity of toxin detection assays ranges between 65 and 85 %, and, therefore, it is recommended that a second specimen be submitted if a negative result is reported when a patient is suspected of having CDAD. Although the cytotoxicity assay is considered the gold standard, it is more labour-intensive and is associated with prolonged turn-around time.

Submission of a stool specimen from asymptomatic patients for "test of cure" is not recommended.

Future methodologies for the laboratory diagnosis of CDAD may include nucleic acid amplification of genes encoding toxins A and B. Studies carried out at MDS Metro Laboratory Services in British Columbia have demonstrated the culture/NAA method to have significantly enhanced sensitivity when compared to EIA alone.

PREVENTION AND TREATMENT

Judicious use of antibiotics and rigorous infection control practices are essential in order to control the incidence of CDAD. Hand hygiene should consist of careful hand washing, rather than alcohol-based rinsing, after exposure to patients with CDAD.

The treatment of CDAD can be summarized as follows:

- Discontinue the inciting antibiotic if possible;
- Replace fluid and electrolyte losses;
- Avoid antiperistaltic drugs;
- Oral metronidazole (250 mg 4 times daily or 500 mg 3 times daily for 10-14 days);
- Oral vancomycin (125 mg to 500 mg 4 times daily for 10-14 days) should be reserved for patients who fail to respond to metronidazole or, according to some experts, for patients with severe infections i.e. WBC greater than 20,000 cells/mm³ or elevated creatinine;³
- Intravenous metronidazole for patients with contraindications for enteral route of administration;

Treatment is not indicated for asymptomatic carriers.

Recurrent CDAD has been reported in approximately 5%-35% of patients following treatment with either metronidazole or vancomycin. Rate of recurrence was as high as 58% in patients described by Pepin *et al.*⁴ The most important risk factor associated with recurrence was advanced age. A variety of treatment options are available for patients with multiple relapses but supporting evidence is limited. Tapered or pulsed dose regimens of oral vancomycin as well as combination therapy with vancomycin and rifampin have been used. Adjunctive therapies may include intravenous immunoglobulin and *Saccharomyces boulardii*. ■

SUMMARY

- *C. difficile* is an important cause of antibiotic associated diarrhea in both inpatients and outpatients
- EIA is the most common laboratory test for detection of *C. difficile* toxin A and B
- Metronidazole is the recommended drug of choice
- Test of cure after treatment is not recommended
- Recurrent *C. difficile* diarrhea occurs in about 5%-35% of treated patients and may require repeated courses of antibiotics
- Antibiotics should be used judiciously to prevent *C. difficile* diarrhea

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- 3 Gerding D. Metronidazole for *Clostridium difficile*-Associated Disease: Is It Okay for Mom? CID 2005;40 (1 June).
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ALLERGY TESTING

SERUM TESTING FOR ALLERGIES



MDS Diagnostic Services offers *in vitro* serum tests to aid in the diagnosis of allergies (also referred to as Specific Allergen IgE testing):

- Total IgE
- Multi-allergen screening panels for allergen types including food, plants and inhalants
- Individual allergen-specific IgE testing to over 450 allergens

General Approach to Allergy Testing

Completion of a detailed history, with particular attention to the effect of environmental factors, such as grass, weeds, trees, animal and foods, is important in the diagnosis of IgE-mediated allergies. If the patient history, in combination with a physical examination, indicates that the patient is likely to be allergic, confirmation of the diagnosis and the identity of the causative allergen(s) may be accomplished using either *in vivo* or *in vitro* methods.

In vivo methodologies include amongst others, skin allergy testing (i.e. skin prick testing or skin scratch testing), food challenges and bronchial provocation tests. While the *in vivo* tests have generally been favoured in the past, research literature has indicated that the *in vivo* and *in vitro* methods of confirming allergic diagnosis are equally effective for most allergens and *in vitro* testing offers several additional advantages.

In vitro Testing

In vitro tests include evaluation of serum total IgE and allergen-specific IgE. Some patients with clinical symptoms may have total IgE levels within the normal range and measurement of total IgE as a screening test is therefore not useful. In these cases and those with poorly defined history, it is useful to measure total IgE in combination with IgE-specific allergens.

	<i>In vivo</i> Testing	<i>In vitro</i> Testing
Advantages	<ul style="list-style-type: none"> • Results immediately available • High sensitivity 	<ul style="list-style-type: none"> • Available to all physicians • Discontinuation of medication not necessary • All patients eligible • Requires a single tube of blood for all allergens • High specificity
Disadvantages	<ul style="list-style-type: none"> • Are not reliable in the very young or aged • Must be performed by specialists and trained personnel • Results affected by patient's propensity to react to allergen • Non-specific reactions occur • Subjective interpretation • Extract quality is not regulated • Patient must discontinue medication (anti-histamines) prior to having test performed • Patients with eczema are not eligible 	<ul style="list-style-type: none"> • Results not available immediately • Turnaround time 24 hours

Multi-allergen screening panels are available for various allergen types, such as those indicated in the table below:

Panel	Allergens Included
Grass Mix >	Orchard, Meadow, Rye, Timothy, June
Tree Pollens Mix 1 >	Oak, Elm, Sycamore, Willow, Cottonwood
Tree Pollens Mix 2 >	Maple, Birch, Beech, Oak, Walnut
Food Mix >	Egg white, Milk, Fish, Wheat, Soya Bean, Peanut
Nut Mix >	Peanut, Hazel nut, Brazil nut, Almond, Coconut
Seafood Mix >	Fish, Shrimp, Blue mussel, Tuna, Salmon
House Dust Mix >	<i>D. pteronyssinus</i> , <i>D. farinae</i> , <i>B. germanica</i>
Inhalent Allergens >	Grasses, Weeds, Trees, Animal, Dust & Mites, Molds, Yeasts

Panels may be helpful to rule-out specific allergen types in patients with unclear histories. The food mix is particularly useful in the pediatric populations, but only as an initial guide. A negative test for peanuts, for example, does not exclude a serious allergy and an oral challenge test may be necessary under carefully controlled conditions to be certain of the diagnosis.

The inhalant allergen panel (offered only in Ontario) detects allergens across several types, but does not include food allergies. Allergy to inhalant allergens is rare in the first year and uncommon until the age of three, but is very prevalent in school-age children. As such, the inhalant allergen panel is most useful in patients greater than 3 years of age.

Allergen panels yielding a positive result should be followed up with measurement of the specific IgE allergens within that panel mix. A negative allergen result in the presence of a positive total IgE result may require a more in-depth case history and specific IgE investigation.

Individual allergen-specific IgE testing is currently available for over 450 allergens. Selection of the specific allergens may be based on the results of the first round of panel testing or, in patients with clear history, selection of single allergens. Allergen-specific IgE results are reported quantitatively and the results can be used longitudinally to determine the effectiveness of therapeutic interventions.

Availability of Testing

To request total IgE, use the standard laboratory requisition.

In Ontario, none of these tests are covered by OHIP but may be covered by private insurance schemes. To order, please complete the MDS 'Allergen Test' requisition, which lists many of the more common single allergens and combinations.

For more detailed information, please refer to:

Ontario: MDS Lab News, October 2001 ■

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