



First reported case of multidrug-resistant *Candida auris* in Canada

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Abstract

Candida auris is a fungal pathogen that has recently emerged as a global threat to public health. It was first described in Japan in 2009 and has since been reported in 17 countries on five continents. This case report describes the first reported case of multidrug-resistant *C. auris* in Canada.

In May 2017, a 64 year-old individual was evaluated for chronic otitis externa. Past medical history included a recent hospitalization in India for elective oral surgery that was complicated by an odontogenic brain abscess. Upon return to Canada, the individual was admitted to a hospital for neurosurgical drainage of the brain abscess and parenteral antibiotics. Early during hospitalization, the patient was identified as a carrier of carbapenem-resistant *Enterobacteriaceae* and was placed on contact precautions. Also early during this hospitalization, a chronic otitis media was managed with placement of a tympanostomy tube with drainage of clear fluid from the ear, which continued through the admission and after discharge to a post-neurosurgical rehabilitation facility. During outpatient follow-up, swabs of the ear discharge cultured *C. auris* that was resistant to fluconazole and amphotericin B. There was no clinical response to ototopical antifungal therapy. Surgical evaluation for management of the otomastoiditis is pending.

There is a potential for *C. auris* to cause infection in health care settings. It can persist in hospital environments, has the potential for transmission and can cause invasive disease. It is difficult to identify and often resistant to antifungal medications. The application of infection prevention and control recommendations can help prevent nosocomial transmission. It is now prudent to consider the risk of *C. auris*, in addition to the known risk of other antimicrobial resistant organisms, in any traveller who has been hospitalized while outside the country. When identified, contacting local public health can assist in the tracking and management of this emerging disease.

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Case

In May 2017, a 64-year-old individual was evaluated for chronic otitis externa. The patient had a two-year history of recurrent ear complaints. Nine months prior to presentation, a general practitioner clinically diagnosed otomycosis based on bilateral ear pain and drainage of serous “cheesy” fluid from one ear. Topical flumethasone pivalate 0.02%-clioquinol 1% was prescribed for eight weeks with resolution of the drainage. Two months later, the patient complained of bilateral ear pain without drainage and was prescribed oral amoxicillin by the same clinician for presumed acute otitis media.

Past medical history included oral surgery conducted in India three months prior to presentation, complicated by an odontogenic brain abscess that resulted in a 24-day hospitalization in India. While hospitalized, a high-resolution computed tomography (CT) scan of the temporal bone demonstrated chronic otitis media with mastoiditis, and osteomyelitis of the mastoid, petrous wall and anterior wall of the middle ear cavity on one side and a mild mastoiditis on the other side. The patient was treated with empiric antibacterial and anti-tuberculosis therapy and, after initial clinical improvement,

returned to Canada and presented to a community hospital for further care. A CT of the brain demonstrated a persistent left frontal abscess and the patient was transferred to a tertiary care hospital for further investigations and management. Early in the tertiary hospital admission, screening rectal swabs identified carbapenem-resistant *Enterobacteriaceae*, so the patient was placed on contact precautions. An aspirate of the brain abscess was obtained for diagnosis; although bacterial, mycobacterial and fungal stains and cultures were negative for organisms, amplification and sequencing of 16S RNA identified *Streptococcus mitis*. The patient was treated with parenteral antibiotics for two months as an inpatient and another month at home, with good clinical and radiographic response. The patient also had a history of emphysema, borderline diabetes mellitus and asymptomatic, early cirrhosis of undetermined etiology.

Shortly after admission to the tertiary hospital in Canada for management of the brain abscess, the patient was also treated by an otolaryngologist for chronic otitis media with a tympanostomy tube, leading to drainage of clear fluid. The drainage continued throughout the remaining three weeks

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of admission to the tertiary care hospital and a one-month admission for post-neurosurgical rehabilitation in a third hospital for complications arising from the brain abscess.

During outpatient follow-up, a swab of the ongoing ear drainage was sent for bacterial and fungal culture. A yeast grew, identified as *Candida auris* by matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry (Bruker MALDI Biotyper System, RUO MBT Compass 4.1.70). Using the CLSI microbroth dilution method, and based on the tentative MIC break-points suggested by the United States (US) Centers for Diseases Control and Prevention (CDC) (1), testing found the *C. auris* sample was resistant to fluconazole and amphotericin B, likely resistant to voriconazole and susceptible to micafungin. (Table 1). The fungus also grew on four repeat swabs of the discharge from the same ear, over a six-week period. Identification of the five isolates as *C. auris* by MALDI-TOF was done by the hospital laboratory. An isolate was sent to a mycology laboratory where drug resistance testing was performed. Whole genome sequence analysis performed by the National Microbiology Laboratory (NML) was consistent with *C. auris*. Further analyses to compare the isolate with global strains are pending.

Table 1: Summary of susceptibility testing of *Candida auris* isolate from the first reported case in Canada

Class	Drug	Tentative MIC Breakpoints ¹	Results from <i>C. auris</i> isolate	Interpretation
Triazoles	Fluconazole	≥ 32µg/mL	128 µg/mL	Resistant
	Voriconazole	N/A ²	N/A ²	Likely resistant ²
Polyenes	Amphotericin B	≥ 2µg/mL	2 µg/mL	Resistant
Echinocandins	Micafungin	≥ 4µg/mL	0.5 µg/mL	Susceptible

Abbreviations: MIC, minimum inhibitory concentration, N/A, Not available

¹ Tentative (MIC) breakpoints for *C. auris* from the United States Centers for Disease Control and Prevention (CDC) (1)

² Until MIC breakpoint is available, CDC suggests considering using fluconazole susceptibility as a surrogate for second generation triazole susceptibility assessment, noting however that isolates that are resistant to fluconazole may respond to other triazoles occasionally

Upon outpatient reassessment by an otolaryngologist, there was evidence of myringitis and otitis externa. The ear canal contained moist white debris, which was removed. A tympanostomy tube was *in situ*, draining a clear discharge; this tube was left in place. The patient was retreated topically with flumethasone pivalate 0.02%-clioquinol 1% drops, but without improvement after two weeks. The patient has been referred to a neurotologist for surgical assessment. Case resolution of the otitis externa and the chronic mastoiditis was pending at the time of the report.

Discussion

This is the first reported case of multidrug-resistant *C. auris* in Canada. *C. auris* was first described in Japan in 2009 (3), and has since been reported in 17 countries on five continents (2,4). Only four *C. auris* isolates from prior to 2009 were identified retrospectively among 15,271 isolates in a global candidemia registry (5), suggesting rapid global dispersal. *C. auris* has already established a firm foot-hold in some healthcare settings. In developing countries, the risk of *C. auris* transmission is compounded by limitations in capacity for fungal identification,

antifungal susceptibility testing and infection prevention and control (IPC). In India, for instance, *C. auris* already accounts for 5% of the isolates implicated in candidemia in intensive care units nationwide (6) and as many as 30% in some centres (7).

Several features of *C. auris* make infection challenging to manage and heighten concern for nosocomial transmission: it can persist on patients and in hospital environments; it is difficult to identify; it can cause invasive disease; and treatment options are limited (1,4,7). Indeed, recalcitrant healthcare-associated outbreaks have been reported from the United Kingdom and the United States (9,10), and genetic studies have implicated closely related (clonal) strains, suggesting effective horizontal transmission (5,7,9,10).

C. auris can persist in hospital environments

The tenacity of *C. auris* has been demonstrated during outbreak investigations in which the organism could be isolated from patients' skin (up to three months following infection) and patient environments (9,14). The capacity of *C. auris* to adhere to polymeric surfaces and form biofilms may contribute to difficulty in eradicating this organism from the environment (15).

C. auris is difficult to identify

Correct identification of *C. auris* can be difficult for clinical microbiology laboratories and this may delay implementation of appropriate IPC procedures. *C. auris* can be misidentified by commercial identification systems such as Vitek-2 (as *C. haemulonii* or *C. famata*) and API-20C (as *Rhodotorula glutinis*, *C. sake* or *Saccharomyces cerevisiae*) (16). *C. auris* can be correctly identified by MALDI-TOF using "research-use only" databases and by sequencing of the internal transcribed spacer and D1-D2 domains (16). Limitations also exist for some antifungal susceptibility testing methods (16); for instance, Vitek-2 may give falsely elevated MICs for amphotericin B and the broth microdilution method may give falsely elevated MICs for caspofungin (16).

C. auris can cause invasive disease

Although the first reported cases of *C. auris* were patients with chronic otomycosis (3,11), most subsequent cases have been healthcare-associated and involved candidemia or other invasive infections (2). Persistent candidemia (lasting up to three weeks after antifungal initiation) and high mortality rates have been observed (7). A murine model of candidemia suggested that *C. auris* was nearly as virulent as *C. albicans*, the predominant cause of invasive candidiasis worldwide (12); precise virulence factors are still being investigated, although some appear to be strain-dependant (13).

Treatment options are limited

Decreased antifungal susceptibility among isolates is a universal feature of *C. auris*. Fluconazole resistance exceeds 90% (5) and reduced susceptibility to voriconazole may approach 50% (2). Tentative breakpoints for the newer triazoles, posaconazole and isavuconazole, are not available, but low MICs suggest that they may have activity against *C. auris* (2). Resistance to amphotericin B occurs in up to 35% of isolates (5) and echinocandin resistance has been reported in 2-8% of isolates (2,5). Resistance to all three major classes of antifungals was reported in 4% of isolates (5).



The optimal management of *C. auris* disease is currently unknown (2). Where invasive disease is involved, systemic antifungal therapy should be guided by results of susceptibility testing. Management of otomycosis and otomastoiditis caused by *C. auris* is even less clear. Evaluations of the efficacy of ototopical agents against *C. auris* have not been published and the options for multidrug-resistant isolates, as in this case, are limited.

Infection prevention and control can limit spread

Infection prevention and control measures can be effective in limiting the spread of *C. auris*. Interim IPC recommendations from the CDC include single rooms and contact precautions for colonized or infected patients, periodic reassessments for ongoing colonization as well as daily and terminal cleaning of surfaces with a disinfectant effective against *Clostridium difficile* spores (See **text box**) (10).

Summary of *Candida auris* Interim Recommendations for Healthcare Facilities from the United States Centers for Disease Control and Prevention (10)

Use standard and contact precautions

Patients in acute care hospitals and nursing homes should be placed in single rooms on Standard and Contact Precautions. Continue Contact Precautions as long as the person is colonized with *C. auris*.

Use a disinfectant effective against *Clostridium difficile* spores

Healthcare facilities that have patients with *C. auris* infection or colonization should ensure thorough daily and terminal cleaning and disinfection of these patients' rooms with hospital-grade disinfectant effective against *Clostridium difficile* spores

Conduct periodic reassessments

Periodic reassessments for presence of *C. auris* colonization (every 1–3 months) can help inform duration of infection control measures. Assessments of colonization should involve testing of, at a minimum, swabs of the axilla and groin and also may include sites yielding *C. auris* on previous cultures.

Provide notification upon transfer

When patients are transferred to other healthcare facilities, receiving facilities should receive notification of *C. auris* infection or colonization and the level of precautions recommended.

Document two negative tests for *C. auris* before stopping infection control procedures

Two or more assessments performed at least one week apart with negative results are needed before discontinuing infection control precautions. The patient or resident should not be on antifungal medications active against *C. auris* at the time of these assessments (wait one week).

Conclusion

This patient is currently clinically stable and awaiting surgical assessment. Best practices for IPC are being carried out in the three hospitals where this patient was cared for, local public health has been informed and regional IPC follow up is underway. Fortunately, as part of the treatment of the brain abscess associated with hospitalization outside the country, routine screening for antimicrobial resistant organisms found carbapenem-resistant *Enterobacteriaceae* and the patient had been placed on contact precautions.

The source of *C. auris* is not yet known, but one source could have been related to the hospitalization in India where *C. auris* is known to be endemic (6,17). Due to the chronicity of ear symptoms and the prior (unconfirmed) clinical diagnosis of otomycosis, the infection may have preceded the patient's most recent travel; however, the patient had been in India prior to the onset of the ear symptoms as well. Genotyping to identify the most likely source of the infection is pending.

As with other antimicrobial-resistant organisms (18), travel-associated infection or colonization from *C. auris* is likely to be increasingly encountered by clinicians. In the United States, two cases of *C. auris* infection were observed in returning travellers who had been hospitalized abroad (10,14). In addition, in a multi-state hospital-associated outbreak in the US, *C. auris* isolates from New York and New Jersey were highly related to one another and were similar to South Asian isolates (10); this suggests the introduction of *C. auris* acquired abroad to healthcare facilities in these states. Anyone who has been hospitalized while outside of the country may be at increased risk for antimicrobial-resistant organisms, including *C. auris*; contact precautions and testing may be indicated. This approach may help contain *C. auris* from nosocomial transmission within and between Canadian healthcare facilities. Alerting local public health can also assist in efforts to track and manage this emerging disease.

Authors' statement

ISS – Conceptualization, Data Collection, Writing - Original Draft, Review and Editing

GWH – Conceptualization, Investigation, Data Collection, Writing - Review and Editing, and Supervision

Conflict of Interest

None.

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