



RAPID RISK ASSESSMENT

Candida auris in healthcare settings – Europe

19 December 2016

Main conclusions and options for response

Due to its propensity to cause outbreaks and its antifungal resistance, *C. auris* poses a risk for patients in healthcare facilities in Europe. Difficulties with laboratory identification, and lack of awareness of this new *Candida* species might result in transmission and outbreaks remaining unnoticed.

C. auris has emerged within a few years of its identification on five continents and caused healthcare-associated infections and outbreaks. There is a need to raise awareness in European healthcare facilities in order for them to adapt their laboratory testing strategies and implement enhanced control measures early enough to prevent further hospital outbreaks.

Options for actions to reduce identified risks: prevention of transmission of *C. auris* in healthcare settings

Laboratory detection of *C. auris*

Isolates of *Candida* species from invasive infections should be identified to species level. Like most other non-*albicans Candida* species, *C. auris* isolates are germ tube test negative and colonies appear pale purple or pink on CHROMagar *Candida* medium. However, they differ from many other species in their ability to grow at temperatures in excess of 42 °C, a characteristic which has potential as a quick screening test, provided that the results are confirmed by other methods.

Because the commercially available biochemical test kits and MALDI-TOF instruments used in clinical laboratories for the identification of yeast isolates may lack *C. auris* in their database, these assays may misidentify *C. auris*. Therefore, further testing must be undertaken if biochemical tests identify yeast isolates from blood cultures as *C. haemulonii*, *C. sake*, *Rhodotorula glutinis*, *Saccharomyces cerevisiae* or other non-*albicans Candida* species.

Correct identification of *C. auris* is possible using the MALDI-TOF commercial instruments with *C. auris* present in the reference profile database or by DNA sequencing of the D1/D2 domain. When the latter tests are not available at clinical laboratory level, referral of non-*albicans Candida* spp. invasive isolates to a reference mycology laboratory is generally advisable. This would be particularly important for hospitals with a suspicion of increased incidence of invasive infection by non-*albicans Candida* species and for patients transferred from facilities reporting *C. auris* outbreaks. In hospitals where capacity for routine speciation of this *Candida* species is not available, monitoring the monthly number of blood cultures positive with non-*albicans Candida* species is advisable as any increase could be an indication of a possible outbreak of *Candida* – possibly *C. auris*.

bloodstream infections. Where *Candida* isolates are tested for antifungal susceptibility, resistance to fluconazole is another characteristic that should alert the laboratory to further identify *Candida* isolates.

Infection control measures

Good standard infection control, including environmental cleaning, adequate reprocessing of medical devices and adequate capacity of microbiological laboratories as well as sufficient capacity of healthcare facilities for patient isolation, are the basis for the prevention of transmission of any pathogen, including *C. auris*, in healthcare settings. Prompt notification of the clinical team and the infection prevention and control/hospital hygiene team is essential to implement infection control precautions in a timely manner.

Targeting patients at high risk for carriage of *C. auris*

Early identification of carriers by using active surveillance cultures in cross-infection epidemic settings is an important tool for outbreak control. Active surveillance cultures should be conducted in accordance with a specified protocol. Sites that could be considered for sampling include nose/throat, axilla, groin, rectum, insertion sites of venous catheters and clinical samples such as urine, faeces, wound drain fluid and respiratory specimens. Further clinical experience will ascertain which sampling sites are the most sensitive to detect and monitor patient colonisation with *C. auris*.

Preventing transmission from patients known to carry *C. auris*

Hospitals should consider enhanced control measures such as contact precautions, single room isolation or patient cohorting, and dedicated nursing staff for patients who are colonised or infected with *C. auris*. Emphasis should also be placed on the terminal cleaning of rooms after discharge of patients who carry, or are infected with, *C. auris*, using disinfectants and methods with certified antifungal activity.

Specific recommendations for outbreak settings

Prompt initiation of an epidemiological investigation, complemented by cross-sectional patient screening and environmental sampling, is useful to establish the source of the outbreak and thus prevent further cases. The detection of even a single case of *C. auris* should trigger such an investigation. Potentially effective enhanced measures for outbreak settings include regular active surveillance cultures for patients admitted to, and resident in, affected wards, cohorting of patients with dedicated nursing staff in separate areas, as well as rigorous environmental cleaning and disinfection. Preliminary hospital experience from the United Kingdom points to the usefulness of chlorine and hydrogen peroxide products, and to limited *in vitro* activity of chlorhexidine against *C. auris*. Education and practice audits to improve compliance of healthcare workers with hand hygiene and contact precautions are important supportive interventions.

Antifungal stewardship

Antimicrobial stewardship programmes aim to improve the clinical effectiveness of antimicrobial treatment and limit antimicrobial resistance by reducing the selective pressure for the development of resistance to currently effective antimicrobials. Although there is no evidence for a specific beneficial effect of antifungal stewardship on the emergence and spread of *C. auris*, it is likely that an environment with high antifungal use will favour the emergence of a multidrug-resistant yeast, such as *C. auris*. Therefore, the implementation of antifungal stewardship is recommended. Fluconazole prophylaxis should be avoided in settings with evidence of *C. auris* transmission.

Prevention of inter-hospital transmission, including cross-border transmission

Admission screening for yeast carriage and pre-emptive isolation of patients who are transferred from, or had recently been admitted to, hospitals in the same or other countries that have detected cases colonised or infected with *C. auris* should be considered in order to reduce the risk of outbreaks subsequent to the introduction of *C. auris* in healthcare facilities. This implies that affected facilities should notify the receiving healthcare facilities and clinicians in the case of patient transfer. Documentation of known colonisation or infection by *C. auris* associated with cross-border patient transfer would optimise the implementation of measures to prevent the international spread of *C. auris*. Moreover, gathering reliable epidemiological data through notification of cases to public health authorities and exchange of information through electronic early warning platforms, such as the Epidemic Intelligence System (EPIS), will enable informed and coordinated risk management actions by public health authorities across the EU/EEA.

Improvement of preparedness in EU/EEA Member States

Member States should consider alerting clinicians and microbiologists in their healthcare facilities and associated reference mycology laboratories to raise awareness for this epidemic fungal pathogen with the aim of adapting laboratory testing practice at primary and reference levels and establishing specific control

measures in a timely manner. National guidelines for laboratory testing and control measures for *C. auris* will enable the implementation of appropriate measures in healthcare facilities. Sharing of outbreak experience and control measures can be facilitated by ECDC.

Improvement of laboratory capacity for detection and antifungal susceptibility testing of *C. auris*

As not all laboratories serving healthcare facilities have the capacity for *C. auris* identification and susceptibility testing of the whole panel of antifungal agents, a national mycology reference laboratory could assist clinical laboratories with the identification of *C. auris*, conduct (and/or assist with) antimicrobial susceptibility testing and epidemiological investigations. The reference laboratory should also issue guidance for local laboratories on how to proceed with difficult-to-identify isolates of *Candida* species and possible *C. auris* isolates, and provide instructions for referring samples for testing and for reporting results.

Retrospective case finding and improved surveillance for *C. auris* infections

To determine the background prevalence of *C. auris* in Member States, it would be advisable to perform a retrospective investigation of the collections of non-*albicans Candida* spp. clinical isolates at national reference mycology laboratories. Member States might also consider laboratory-based notification of *C. auris* invasive infections and prospective data collection at national level. Surveillance systems for healthcare-associated infections should be updated to include *C. auris* in the list of reportable pathogens associated with healthcare-associated infections.

Source and date of request

ECDC internal decision, 8 December 2016.

Public health issue

Candida auris is an emerging fungal pathogen associated with outbreaks of invasive infection, including candidemia, in healthcare settings worldwide. In Europe, hospital outbreaks caused by *Candida auris* have occurred in the UK and Spain. These hospital outbreaks have been difficult to control despite enhanced control measures.

C. auris can cause invasive infections in severely compromised patients, and most *C. auris* isolates are resistant to fluconazole. Resistance to other antifungal agents has been reported, and multidrug-resistant *C. auris* isolates with resistance to all three main classes of antifungals have been described. Unlike other *Candida* species, *C. auris* seems to have a high propensity for patient-to-patient transmission in healthcare settings, possibly related to environmental contamination, or transient person or device colonisation. Commercially available laboratory tests used by clinical laboratories might fail to identify *C. auris*.

Consulted experts

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Disease background information

Invasive candidiasis is the most common fungal disease in hospitalised patients [1]. In the *ECDC point prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals 2011–2012*, *Candida* spp. was the fifth most common pathogen associated with bloodstream infections, isolated in 7.4% of all documented cases [2]. While *C. albicans* remains the predominant cause of invasive candidiasis, there has been a shift towards an increasing proportion of non-*albicans Candida* species such as *C. glabrata* in recent years [1,3].

Candida auris is a newly emerging yeast that was first described in 2009 after isolation from the ear canal of a Japanese patient [4] and has subsequently been associated with invasive infections and outbreaks in healthcare

settings. *C. auris* infections have been reported from South Korea [5], South Africa [6], India [7], Pakistan [8], Kuwait [9], Venezuela [10], Israel [11], Kenya [12], the UK [13] and the USA [14]. The US Centers of Disease Control and Prevention (CDC) report on their website that *C. auris* has also been identified in Colombia [15], and a published laboratory-based study has included isolates from Brazil [16].

C. auris infections include bloodstream infections, wound infections and ear infections [4,5,9,13]. The majority of the published cases have been *C. auris* bloodstream infections. *C. auris* has also been isolated from urine [14], though this may have represented carriage rather than infection.

Non-*albicans* *Candida* spp. have emerged in healthcare settings worldwide, presumably related to the use of prophylactic antifungal drugs in high-risk populations [17], but *C. auris* seems to be unique in its propensity to be transmitted between patients and cause outbreaks in healthcare settings. A number of hospital outbreaks has been reported and several molecular studies confirming intra- or interhospital transmission of *C. auris* have been published [7,10,13].

Antifungal resistance

Most of the described *C. auris* isolates worldwide were resistant to fluconazole, but their susceptibility to other azoles, to amphotericin B, and echinocandins, varied depending on the isolate. A study including 54 *C. auris* isolates from three continents found that 50 (93%) isolates were resistant to fluconazole, 19 (35%) were resistant to amphotericin B, and four (7%) were resistant to echinocandins [8]. Overall, 22 (41%) isolates were resistant to ≥ 2 classes of antifungals, and two isolates were resistant to three classes of antifungals [8].

Laboratory identification and antimicrobial susceptibility testing

C. auris cannot be identified based on microscopy or growth on chromogenic agars [18]. In addition, biochemical testing performed with Vitek-2, BD Phoenix, MicroScan or API strips may misidentify *C. auris* as being another *Candida* species or yeast, for example as *C. haemulonii*, *C. famata*, *C. lusitanae*, *C. guilliermondii*, *C. parapsilosis*, *C. sake*, *Rhodotorula glutinis* or *Saccharomyces cerevisiae* [6,15,18,19]. Nevertheless, matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry can reliably differentiate *C. auris* from other *Candida* species as long as *C. auris* is included in the reference database and care is taken regarding the extraction method [19,20]. Alternatively, molecular identification of *C. auris* can be performed by sequencing internal transcribed spacer and D1/D2 regions [7]. In addition to the above-mentioned difficulties with laboratory identification, *C. auris* might remain undetected if laboratories do not attempt identification of *Candida* isolates at the species level, but rather report them as non-*albicans* *Candida* species.

Minimum inhibitory concentration (MIC) breakpoints for *C. auris* have not yet been established, therefore breakpoints of related *Candida* species have been used for the interpretation of antifungal susceptibility testing [8]. The EUCAST broth microdilution method can be used to test for fluconazole susceptibility that can be interpreted with non-species-related clinical breakpoints [21].

Active surveillance cultures are an important part of outbreak control measures. In the 2015/2016 UK outbreak, contact patients were screened for *C. auris* at the following sites: nose, axilla, groin, throat, rectum/faeces, vascular line and drain exit sites as well as from clinical samples such as urine, wound, drain fluid and respiratory specimens [13].

Event background information

Cases and outbreaks of *C. auris* in EU/EEA Member States

United Kingdom

An outbreak of *C. auris* infection at a 296-bed cardio-thoracic surgery centre was reported in October 2016 [13]. Over a 16-month period from April 2015 to July 2016, 50 cases of *C. auris* infection occurred in this centre. Twenty-two (44%) of these cases required antifungal treatment, nine (18%) of which had a bloodstream infection (candidemia) [13].

Spain

An outbreak of *C. auris* bloodstream infections occurred in 2016 in the surgical intensive care unit of a hospital in Spain. After identification of the first case by sequencing in April 2016, 33 cases of *C. auris* bloodstream infection were detected by the end of November 2016. The screening of about 100 healthcare workers did not return any positive cultures. The implemented control measures included contact precautions, active surveillance for yeasts, decolonisation baths with chlorhexidine, preventive isolation of patients with a positive culture for yeasts, cohorting

of cases with dedicated nursing staff, use of disposable chlorhexidine alcohol wipes before intravenous catheter manipulation, and cleaning of environmental surfaces three times per day with disposable chlorhexidine towels. The incidence of *C. auris* bloodstream infections decreased after these measures were applied, and 95% compliance with hand hygiene was achieved.

Other EU/EEA countries

In Norway, one isolate of *C. auris* resistant to fluconazole was detected among isolates from invasive *Candida* infections sent routinely to the national reference laboratory for characterisation. Although this case of *C. auris* infection was diagnosed in Norway, the infection was probably acquired abroad as the concerned patient was transferred directly from a hospital outside of the EU/EEA.

The German national reference centre for invasive fungal infections reported on its website that it detected an isolate of *C. auris* resistant to fluconazole isolated from a blood culture in November 2015 [22].

ECDC threat assessment for the EU

Impact on human health

Healthcare-associated *C. auris* infections

Healthcare-associated *C. auris* bloodstream infections have mainly affected patients with severe underlying diseases and immunosuppression, such as patients with diabetes mellitus, chronic kidney disease, HIV, solid tumours and haematological malignancies [7,14]. Neonates have also been affected [8].

Patients who developed a *C. auris* infection had frequently been exposed to medical procedures and devices including central venous and urinary catheters, surgery, treatment with broad-spectrum antibiotics, and admission to intensive care units [7,17]. Treatment with systemic antifungals prior to *C. auris* infection has also been reported for a proportion of patients [8].

Limited treatment options

Fluconazole and the echinocandins are the antifungal agents most commonly used for the treatment of *Candida* bloodstream infection (candidemia). Both are better tolerated than amphotericin B, which is given less often due to the risk of toxicity. Fluconazole cannot be used for treatment of *C. auris* as nearly all isolates are resistant. Resistance to other antifungals seems to be more variable; however, isolates with resistance to all three major classes of antifungals (azoles, echinocandins, and amphotericin B) have been described outside of Europe [15]. This is worrisome as it seriously limits available treatment options for patients with invasive *C. auris* infections.

Mortality

The case-fatality rate of *Candida* bloodstream infection has been reported to be around 30 to 40% in previous studies, even in patients receiving antifungal treatment [1,23]. There is currently limited information on the case-fatality rate for *C. auris* bloodstream infections due to the small number of patients included in published case series or outbreak descriptions. A study published in 2013 reported case-fatality rates for *C. auris* bloodstream infections of 33% for all patients and 57% for the subgroup of patients admitted to intensive care units, but these rates might be attributable to the severity of underlying diseases in these patients [7]. In the UK outbreak, no fatalities could be directly attributed to *C. auris* infection [13]. In a recent *in vitro* study, the pathogenicity of the most virulent *C. auris* strains was comparable to that of *C. albicans* [24].

Potential for spread

Outbreaks and spread in healthcare settings

Based on molecular typing, transmission of *C. auris* between separate wards that did not share healthcare personnel has been reported from a hospital in India [7]. Inter-hospital transmission of *C. auris* has also been reported in the same study [7]. The majority of *C. auris* infections reported in the published literature were acquired in healthcare settings. In addition, molecular typing has shown that *C. auris* isolates from the same geographical areas were closely related, which suggests clonal spread. The capacity for intra- and interhospital spread combined with multi-drug resistance suggest that *C. auris* has the typical characteristics of a healthcare-associated pathogen and that further spread in healthcare settings should be expected.

C. auris outbreaks have been difficult to control, with cases in the affected hospitals being detected over periods longer than a year [10,13]. Widespread environmental contamination of surfaces and equipment surrounding patients carrying *C. auris* has been demonstrated [13,14]. Carriers also represent an important reservoir, and continuous carriage for up to three months after initial isolation of *C. auris* has been documented [14]. Decolonisation has been attempted in one outbreak, but patients remained carriers despite daily chlorhexidine

washes [13]. There is currently insufficient evidence regarding decolonisation regimens and their effectiveness to eradicate *C. auris* carriage.

Clinicians and infection control staff, even if experienced in the control of multidrug-resistant bacteria, may not expect outbreaks of *Candida* species. Combined with the additional difficulties in laboratory identification, this lack of awareness might result in outbreaks of *C. auris* remaining unnoticed or only being detected after a number of patients developed severe infections.

The CDC had issued a clinical alert to US health facilities regarding the global emergence of *C. auris* in June 2016 [15]. Public Health England published a notification on *C. auris* identified in England as well as a document entitled *Guidance for the laboratory investigation, management and infection prevention and control for cases of Candida auris* [18,25].

Cross-border transmission

Due to the difficulties with laboratory identification, little is known about the prevalence of *C. auris* in different regions of the world. Nevertheless, *C. auris* isolates, cases and outbreaks have now been reported from five different continents: Europe, Asia, North America, South America, and Africa. The case reported by Norway is presumed to have been imported from a country outside of the EU/EEA, and it is likely that there is a risk of importation of *C. auris* via hospital transfer of patients and subsequent outbreaks in healthcare settings in the EU/EEA. Indeed, a recent study has shown that isolates of *C. auris* present in the UK have several diverse geographic origins, suggesting multiple introductions into the country [26].

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