Journal de Mycologie Médicale xxx (2018) xxx–xxx

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General review

Candida auris: An emerging drug resistant yeast – A mini-review

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ARTICLE INFO

Article history:
Received 12 March 2018
Received in revised form 20 June 2018
Accepted 20 June 2018
Available online xxx

Keywords:
Candida auris
Antifungal
Epidemiology
Treatment
Multi-drug resistance
Prevention
Control strategy

ABSTRACT

Candida auris is an emerging fungal pathogen responsible for nosocomial invasive infection outbreaks on five continents. Large healthcare-related outbreaks of *C. auris* infection and colonization have been reported from different countries. Whole genome sequence analysis identified strong phylogeographic *C. auris* clades specific to particular geographical areas suggesting transmission of particular clades within countries. However, the mode of transmission within the healthcare environment is not clear and is likely to be multifactorial. The emergence of *C. auris* is alarming because this organism can harbor or develop multidrug resistance. This explains why *C. auris* infections are difficult to treat. In addition, difficulties in its identification in the routine diagnostic laboratory have a significant impact on outbreak detection and management. This mini-review highlights the available literature on *C. auris*, with particular insight into its epidemiology and the problems caused by its antifungal resistance.

Contents

1. Introduction

Candida auris is an emerging, multi-drug resistant, fungal pathogen responsible for nosocomial invasive infections [1–4]. *C. auris* was first described from an external ear canal drainage specimen from a Japanese patient in 2009 [5]. Although initially presumed to be a rare pathogen, this species has been increasingly detected throughout the world in less than a decade following its first isolation. In June 2016, the Centers for Disease Control and Prevention (CDC) published an alert for all clinicians, laboratorians, and public health authorities to report isolation of *C. auris* in patients in the United States [1]. The global epidemiology of this yeast is not well known. Specifically, the incidence and prevalence rate have not yet been available as this species is difficult to identify using conventional biochemical methods [6–9].

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https://doi.org/10.1016/j.mycmed.2018.06.007
1156-5233/

Please cite this article in press as: Bidaud AL, et al. *Candida auris*: An emerging drug resistant yeast – A mini-review. Journal De Mycologie Médicale (2018), https://doi.org/10.1016/j.mycmed.2018.06.007

This mini-review summarizes important features of *C. auris* epidemiology, identification, antifungal profile, treatment, prevention, and control strategies.

2. Taxonomy–Phylogenetic

C. auris closest phylogenetic relationship is with *C. haemulonii* which can lead to misidentification problems [7,9]. *C. auris* genome has a size range between 12.3 and 12.5 Mb with 8527 predicted genes [10]. Draft genome comparisons revealed that more than 99.5% of the *C. auris* genomic reads did not align to the current draft genome sequences of *C. albicans, C. lusitaniae, C. glabrata* and *Saccharomyces cerevisiae*, which suggests *C. auris* is highly divergent at the whole genome level [10]. Among the sequenced *C. auris* isolates, the initial Japanese isolate is closest to the hemiascomycete species *Clavispora lusitaniae* [3,5,10]. When compared to each other, *C. auris* isolates can be grouped into geographic-specific clusters [6,11].

The CDC described the epidemiology of *C. auris* infection using whole genome sequencing (WGS) of 47 isolates collected from Pakistan, India, South Africa and Venezuela during 2012-2015 and the type specimen from Japan. Phylogenetic analysis identified a strong phylogeographic structure comprising 4 distinct *C. auris* clades. These clades were separated by tens of thousands of single-nucleotide polymorphisms and represented distinct geographic regions whereas WGS analysis demonstrated low genetic diversity among isolates within each clade [6,11]. A recent WGS study from India with 5 isolates also reports similar results of low genetic diversity in *C. auris* from different hospitals in India [12].

3. Epidemiology

C. auris earliest known infections have been documented in South Korea in 1996 [1,13]. A retrospective review of the SENTRY isolate collection, with 15271 isolates of *Candida* spp. from 4 continents identified a 2008 *C. auris* isolate from Pakistan, which had not been previously recognized. However, to our knowledge, no other *C. auris* isolates from 1996–2009 have been reported suggesting that *C. auris* was not simply misidentified previously but indeed rare before 2009 [2]. In 2011, report of three South Korean patients with fungemia described *C. auris* invasive nosocomial infections for the first time [13]. Between 2004 and 2006, 15 unusual yeast isolates with phenotypic similarity to *C. haemulonii* were recovered in culture from ear samples in 5 hospitals in Korea which were later confirmed as *C. auris* [14,15]. These reports were followed by two reports of *C. auris* candidemia in several hospitals in India which emphasized the occurrence of clonal multi-drug resistant *C. auris* strains in the health care settings [16,17]. In Europe, two large outbreaks have been reported, one in a London cardio-thoracic center between April 2015 and July 2016 [18] and one in a University hospital in Valencia, Spain, between April 2016 and March 2017 [19,20]. The first outbreak of *C. auris* in America was reported in the intensive care unit of Maracaibo tertiary hospital, Venezuela from March 2012 to July 2013. The outbreak reported 18 patients and all isolates were first identified as *C. haemulonii* but later confirmed as *C. auris* by ITS sequencing [21]. Many cases of infections due to *C. auris* have been reported in several cities of Colombia since 2013. Between 2015 and 2016, the city of Barranquilla reported 27 isolates of *C. auris*. Also, an outbreak in a pediatric intensive care unit in Cartagena, in August 2016 reported five cases of *C. auris* disseminated infection. At first, these isolates were identified as *C. albicans, C. guilliermondii*, and *Rhodotorula rubra*, before being confirmed as *C. auris* by MALDI TOF Mass Spectrometry (MALDI-TOF MS) [21]. In the United States, *C. auris* isolation was reported as part of a surveillance program in 2013 [1,21,22]. Infections due to *C. auris* have also been reported from several European countries like Spain [23], Switzerland [24], Germany [25], Norway [26]. In response to the ECDC *C. auris* survey, 620 *C. auris* cases were reported from six EU/EEA countries for the period 2013–2017. The European countries reporting *C. auris* cases includes Spain ($n = 388$), the UK ($n = 221$), Germany ($n = 7$), France ($n = 2$), Belgium ($n = 1$) and Norway ($n = 1$) [27]. Austria detected one case in January 2018. The majority of cases were reported as colonisation ($n = 466$; 75.2%), while a bloodstream or other type of infection was reported in 150 (24.2%) cases. Majority of *C. auris* reports have originated from India, Central America, Kuwait, South Africa, Israel, and Oman [16,17,28–32]. Recently, a single isolate of *C. auris* is reported from China [33]. The first case of *C. auris* infection in France has been reported recently [34].

4. Risks factors

Risk factors for *C. auris* infection appear to be similar to infections from *Candida* spp. in general. These include immunosuppressed state, significant medical comorbidities, central venous catheters, urinary catheters, recent surgery, parenteral nutrition, exposure to broad spectrum antimicrobials, diabetes mellitus, malignancies, intensive care unit admission and specialized care residence [2]. The overall crude in-hospital mortality rate of *C. auris* candidemia ranges from 30% to 60% and infections typically occur several weeks after admission [4].

5. Phenotypic characteristics

C. auris infections are probably underestimated due to frequent misidentification of *C. auris* as *Candida famata, C. haemulonii, Candida sake, Saccharomyces cerevisiae* or *Rhodotorula glutinis* by commercial identification techniques in clinical laboratories [6–9].

The correct identification requires either MALDI-TOF MS or molecular identification based on sequencing the D1-D2 region of the 28S ribosomal DNA [8]. However, MALDI-TOF MS can accurately identify the organism, provided that *C. auris* is included in the library. Laboratories should check with the manufacturer for the presence of *C. auris* in their database. Confirmation of their presence could then be tested by obtaining reference strains [4].

Phenotypically, *C. auris* is difficult to be distinguished from other *Candida* species. *C. auris* forms light pink to beige/white colonies on chromogenic media (CHROMagar Candida) and white to cream coloured colonies on Sabouraud. Microscopically, the isolates of *C. auris* are oval without pseudohyphae and are germ tube negative. However, pseudohyphae may be formed in the presence of sodium chloride [33]. *C. auris* demonstrates thermotolerance, growing optimally at 37 °C and maintaining viability up to 42 °C [9]. In contrast, *C. haemulonii* and *C. duobushaemulonii* isolates reveal pseudohyphae with blastoconidia and do not grow at 42 °C. *C. auris* assimilates N-acetylglucosamine, succinate and gluconate whereas *C. haemulonii* and *C. duobushaemulonii* do not assimilate the same sugars [8].

Recently, PCR and real-time PCR assays for identification of *C. auris* and related species (*C. duobushaemulonii*, *C. haemulonii*, and *C. lusitaniae*) have been evaluated.

The identification results from the assays were 100% concordant with DNA sequencing results. These molecular assays overcome the deficiencies of existing phenotypic tests to identify C. *auris* and related species [35].

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