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CASE REPORT

Successful control measures to treat the transmission of *Candida auris* in Northern Italian Hospital

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SUMMARY

Candida auris has emerged globally as a multidrug-resistant health care-associated fungal pathogen. In the literature, nosocomial outbreaks are reported worldwide. In addition, *C. auris* diffusion occurs in high-dependency settings with infections typically affecting critically ill patients, resulting in life-threatening disease. We describe the first documented case of *C. auris* in northeastern Italy and the measures applied to contain the transmission that led to zero collateral infections.

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INTRODUCTION

Candida auris is an emerging drug-resistant fungus that is increasingly associated with hospital outbreaks worldwide (Schelenz *et al*., 2016). It was isolated for the first time in 2009 in Japan (Du *et al*., 2020) and the earliest known *C. auris* strain was discovered in 1996 in South Korea (Kwon *et al*., 2019).
The multidrug resistance profile of most *C. auris* strains is an emerging problem (Ademe *et al*., 2020) extended to all antifungal drug classes in variable proportions (Sekyere *et al*., 2018).
In Europe, outbreaks have been reported in the United Kingdom (UK), Germany, Spain, Greece and Italy (Schelenz *et al.*, 2016; Di Pilato *et al*., 2021; Geremia *et al.,* 2023; Hinrichs *et al.,* 2022). In Italy, several cases and outbreaks have been reported in Liguria and Piemonte (Geremia *et al*., 2023).
Most *C. auris* cases occur in critically ill patients and are associated with high rates of resistance, phenotypes and clinical treatment failures (DiPilato *et al*., 2021).

Key words:
Candida auris, multidrug resistance, infection control, public health.

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METHODS

Settings

The imported *C. auris* case was identified on June 24, 2022 in the Geriatric ward of Ospedale "Dell'Angelo", Venice, Italy. *C. auris* screening surveillance was conducted on geriatric patients, and on health and hospital cleaning service personnel with *C. auris* contact cases from June 17 to 24, 2022.
The Geriatrics unit contained 41 beds, including 16 single and 14 double rooms. Among the 16 single rooms, eight had shared bathroom facilities.

Microbiology

Blood, urine and bronchial aspirate cultures were performed. In addition, the *C. auris* case and contacts were tested with a single axilla and groin swab for yeast identification because axilla and groins appear to be the highest-yield site to swab to identify patients colonized with *C. auris*, as indicated by the Centers for Disease and Control Prevention (CDC) (https://www.ecdc.europa.eu/en/publications-data/core-competencies-infection-control-and-hospital-hygiene-professionals-european).
Specimens for routine fungal analysis were inoculated on Brilliance™ Candida Agar Base (Thermo Fisher Scientific™). The cultures were incubated at 37°C. Yeast isolates were identified with Matrix-Assisted

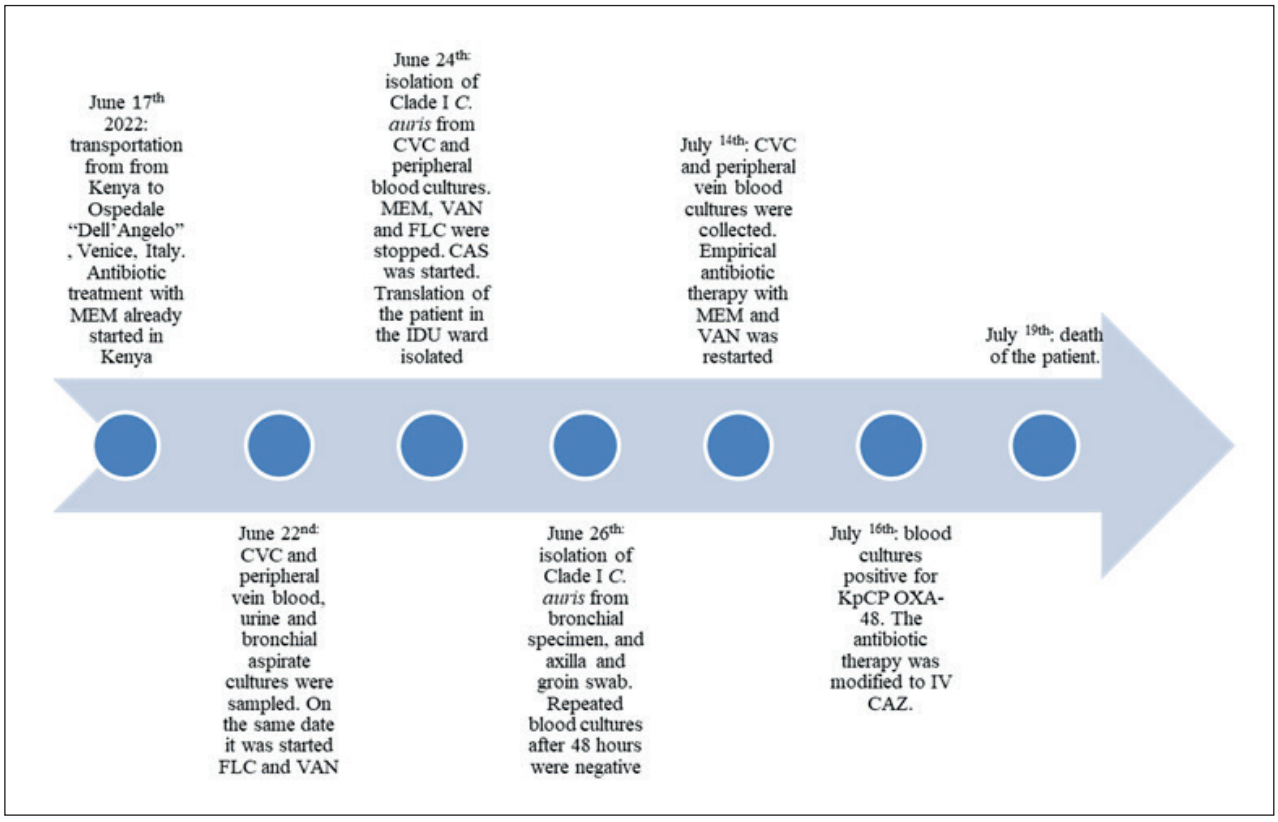

Figure 1 - *Timeline of clinical isolation, and the antibiotic and antifungal treatments.*

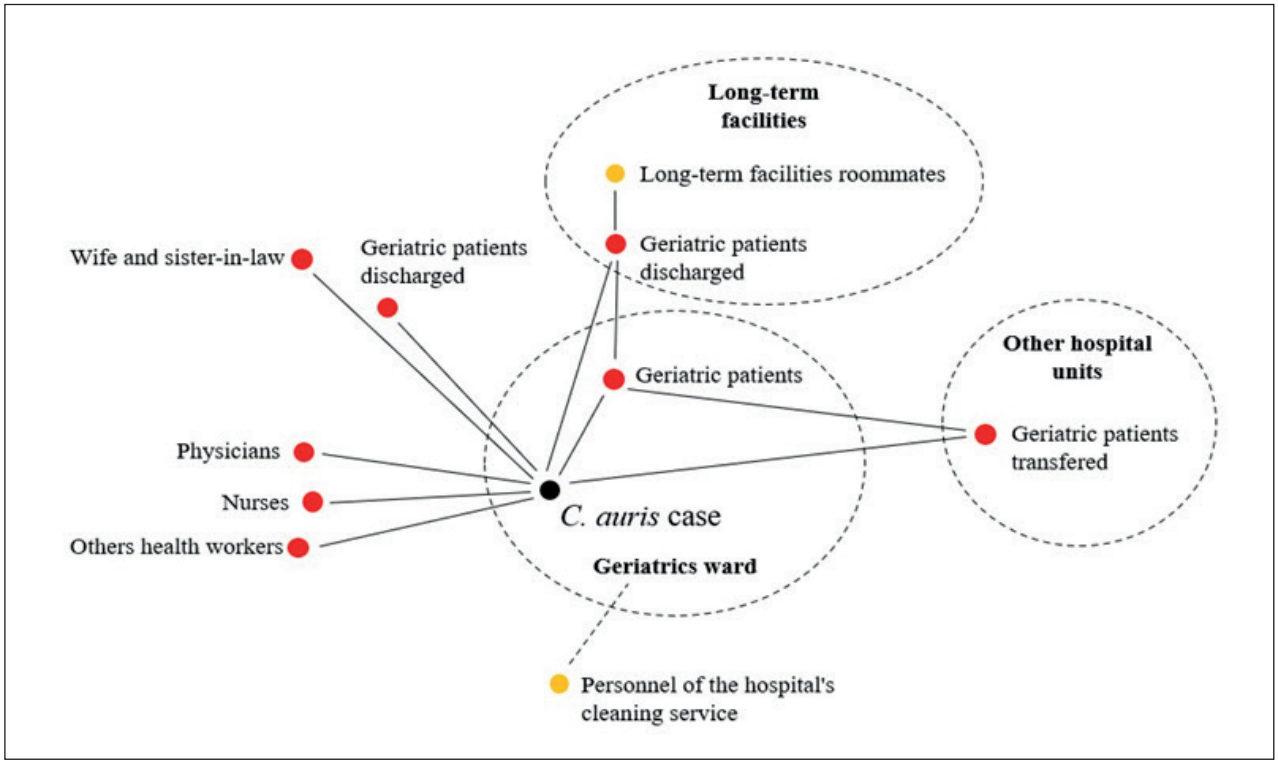

Figure 2 - *C. auris contact tracking. Contacts tested for C. auris colonization. Black point = C. auris case, red point = close contact of C. auris case, and yellow point = environmental contacts and contacts of geriatrics patients that had contact with C. auris case*

Laser Desorption Ionization Time-of-Flight (MALDI-TOF) technology. Susceptibility testing was performed using broth microdilution MICRONAUT-AM (MERLIN Diagnostika GmbH, Bornheim, Germany).

Contact tracking

Patients hospitalized in the Geriatric ward from June 17 to 24, 2022 were all considered contacts, extending the monitoring and the surveillance even to the assistance staff, including health personnel who provided medical, nursing, or personal hygiene assistance, following a precautionary principle and fulfilling the ECDC Guidelines (https://www.ecdc.europa.eu/en/publications-data/core-competencies-infection-control-and-hospital-hygiene-professionals-european). For contacts discharged to long-term care facilities, we conducted an additional screening on the contacts' roommates.

The wife and sister-in-law of the patient in the exam were considered close contacts and monitored for *C. auris* follow-up.

Personnel of the hospital's cleaning service was also tested for *C. auris*. Labor union representatives were involved in the context of sharing the information with the personnel, to get support in the operators' monitoring.

The contact tracking analysis is summarized in *figure 2*.

Contacts follow-up

All the contacts were subjected to a single axilla and groin swab every week for two months. Screening also continued in case of discharge or transfer to other hospital units or long-term care facilities.

After this screening period, if no development of *C. auris* colonization was found in the contacts, they were considered negative and dropped out of follow-up.

Hygiene measures

After the *C. auris* case identification, the patient was isolated in a private room in the IDU. Health professionals adopted contact and droplet precautions. Routine daily cleaning and disinfection of the patient's room were performed. Medical devices (thermometer, stethoscope, etc.), reserved only for the C. auris case were also adopted.

After disinfection, all the surfaces were buffered to check for a potential environmental reservoir.

RESULTS

Clinical case

An 82-year-old male was hospitalized on May 24, 2022 in Nairobi Hospital in Kenya for abdominal pain and icterus caused by cholangitis and suspected duodenal neoplasia. During the hospitalization, he was subjected to endoscopic retrograde cholangiopancreatography (ERCP), which excluded the presence of small intestine neoplasia. The procedure was complicated by septic and cardiogenic shock.

The patient was transferred to the Intensive Care Unit (ICU) and the cardiogenic shock determined a post-anoxic coma. In ICU, a broad spectrum empirical antibiotic therapy was started with Meropenem (MEM) 1 g IV every 8 hrs. In addition, a central venous catheter (CVC) and a bladder catheter were placed. The patient showed a progressive improvement in his clinical condition, but a tracheostomy was necessary due to the post-anoxic damage which caused paraparesis and anomia.

On June 17, 2022, he was transported from Kenya to Ospedale "Dell'Angelo", Venice, Italy. He was recovered in a single room with a personal bathroom in the Geriatric ward.

On June 22, fever appeared despite the ongoing antibiotic treatment. The blood exams showed that C reactive protein (CRP) raised to 14.08 mg/dL while the procalcitonin was still negative. Therefore, FLC 800 mg (loading dose), followed by 400 mg IV every 24 h and Vancomycin (VAN) 1 gr IV every 12 h, were started. Furthermore, CVC and peripheral vein blood, urine and bronchial aspirate cultures were sampled.

Although the FLC was added, the patient didn't improve. On June 24, Clade I *C. auris* was isolated from CVC and peripheral blood, and two days later from bronchial aspirate cultures. Consequently, antifungal therapy was modified to CAS 70 mg IV (loading dose), followed by 50 mg IV every 24 h. MEM and VAN were stopped. CVC and bladder catheter were replaced. The patient was transferred to the IDU ward in a private room.

The day after, the antifungal antibiogram reported the following Minimum Inhibitory Concentrations (MIC): anidulafungin MIC 0.0625 µg/ml, amphotericin B MIC 0.5 µg/ml, caspofungin MIC 0.125 µg/ml, flucytosine MIC 0.0625 µg/ml, micafungin MIC 0.125 µg/ml, fluconazole MIC 128 µg/ml.

Subsequent blood cultures were collected and were negative for fungi. Axilla and groin swab was performed and resulted positive for *C. auris*.

Fundus oculi and echocardiography were required but not performed because he had a worsening clinical condition. The patient developed septic shock two weeks after the beginning of CAS. New CVC and peripheral vein blood cultures were collected. Empirical antibiotic therapy with MEM and VAN was restarted.

After a couple of days, blood cultures were positive for OXA-48 carbapenemase-producing *K. pneumoniae* (KpCP OXA-48). The antibiotic therapy was modified to IV Ceftazidime-Avibactam (CAZ) 2.5 gr every 8 h infused over 3 h. Unfortunately, after a few days, the patient died.

Infection prevention and control measures

After the identification of *C. auris*, an emergency multidisciplinary team was convened. The team included members from Department of Medical Direction, Hygiene and Public Health Service (SISP), IDU, Unit of Geriatrics, Unit of Microbiology and Virology, hospital's pharmacy and cleaning service.

The case notification was sent to the regional Prevention, Food Safety, Veterinary Department and the Italian Ministry of Health. In Italy, this is the first case of *C. auris* infection reported in the Veneto region.

Daily meetings were conducted to plan contact follow-up and preventive measures to be implemented.

C. auris patient's contact follow-up

We conducted a *C. auris* screening on 70 patients hospitalized in the Geriatric ward from June 17 to 24, 2022.

We also screened 25 roommates for patients under *C. auris* swab follow-up discharged from the same period from geriatrics to long-term care facilities.

The follow-up was reserved for 30 healthcare professionals and 7 members of the cleaning service personnel that could have had close contact with the *C. auris* case.

DISCUSSION

C. auris can spread among patients via contact with contaminated surfaces, and differentiates *C. auris* from traditional *Candida* spp. This characteristic represents a fundamental problem for the Healthcare system (Kohlenberg *et al*., 2018).

The Global Health Security Agenda (GHSA) was established in 2014 in response to the global threat that infectious diseases pose in our increasingly interconnected world. Our imported case of *C. auris* is a clear example of such a phenomenon. In our case, NGS identified a Clade I *C. auris*, which was the most widespread and found in ten different countries, including Kenya (Kanyua *et al*., 2020; Chow *et al*., 2020). Clade I *C. auris* has a higher percentage of BSI compared to Clade II and Clade III. Additionally, some reports suggested that Clade I *C. auris* has the highest rates of multidrug resistance (MDR) and is the only clade that could express extensive drug resistance (XDR) to all three major classes of antifungals.

The XDR Clade I *C. auris* was detected in two geographic areas (United Arab Emirates and Kenya) (Chow *et al*., 2020). Moreover, the link between the belonging Clade and mortality was studied, but no correlations were found (Chen *et al*., 2020). Despite this evidence, the development of BSI is a risk factor itself for increased mortality, so the belonging Clade has clinical relevance.

We decided to screen so many people because there was a time window in which the patient was colonized by *C. auris* but such colonization was not known. Although the patient was placed in an isolation room and adequate preventive measures were taken, this precaution was an additional measure due to the high ability of *C. auris* to spread among patients via contact with contaminated surfaces. No secondary *C. auris* case or environmental reservoir was found.

Our case showed that adequate preventive measures, initial isolation in a private room, and correct surface disinfection reduced the risk of *C. auris* spread. Constant and daily multidisciplinary meetings helped the close adherence to CDC recommendations.

C. auris is often resistant to FLC, with variable resistant rates from 44.29% to 91% (Sekyere *et al*., 2018; Chow *et al*., 2020; Chen *et al*., 2020). In the invasive candidemia of unknown *Candida* spp. the IDSA guidelines suggest an initial treatment with echinocandins, such as CAS. Initial treatment with an echinocandin is supported by its potent fungicidal activity, favorable safety profile, and low resistant rates in *C. auris*. (Pappas *et al*., 2016). For that reason, we switched the antifungal therapy from FLC to CAS. One of the most challenging problems is that there are currently no established *C. auris*-specific susceptibility breakpoints. At this time, the correlation between microbiologic breakpoints and clinical outcomes is unknown. For that reason, the interpretation of our antifungal antibiogram was based on the CDC's general guide for breakpoints resistance definition (https://www.cdc.gov/fungal/candida-auris/c-auris-antifungal.html). In our case, the susceptibility to echinocandins and the resistance to FLC was confirmed. The subsequent collected blood cultures were negative for *C. auris* isolation, highlighting the effectiveness of the therapy. Unfortunately, we could not perform fundus oculi and echocardiography because the patient had a worsening clinical condition.

The multisite colonization of *C. auris* is an independent risk factor for the development of *C. auris* candidemia (Boriano *et al*., 2022). In our case, we isolated *C. auris* from three different sites, collecting blood, respiratory and skin specimens (the urinary specimen was negative).

The isolation of *C. auris* in multiple specimens collected from the patient, including bloodstream, underlines a high probability of a long-standing previous colonization. This assumption is strengthened by the fact that the growth of the pathogen took only four days after hospitalization at the Ospedale "Dell'Angelo," highlighting a high mycotic load. Furthermore, literature reports that multiple clusters of *C. auris* infections occurred in the Nairobi Hospital (Chow *et al*., 2020).

The mortality of *C. auris* fungemia is not more significant if compared to *C. albicans* bloodstream infections (BSI) (Samuel *et al*., 2023). However, attributable mortality is difficult to determine due to comorbidity burden and concomitant acute disease

states (Briano *et al*., 2022). As in our case, the patient had a critical illness, including post-anoxic coma after cardiogenic shock, recurrent septic shock, and concomitant KpCP OXA-48 BSI, which determined death. The rectal swab for screening of MDR pathogens performed at the admission in our Hospital was negative, so we deduce that the KpCP OXA-48 is the result of the selective pressure exerted by the prolonged therapy with MEM.

More studies are needed to evaluate actual *C. auris* virulence and the pathogenetic role of other *Candida* spp., such as *C. albicans* (Forsberg *et al*., 2019).

Our case has some limitations. First of all, we didn't perform a screening for *C.* auris colonization at the time of admission. Another limitation is that we could not perform fungal embolism investigations, such as fundus oculi and echocardiography. These diagnostic tests were postponed due to the worsening clinical condition.

In addition, the lack of interpretative clinical breakpoints for *C. auris* is one of the major problems to consider. Therefore, studies are necessary to evaluate this critical diagnostic aspect.

In conclusion, correct preventive measures and their continuous monitoring by a multidisciplinary team contained the potential spread of *C. auris*. More in detail, early actions were probably fundamental to limit the infection to just one patient, pointing out the fact that the spread in clusters could be linked to an unknown colonization. Following this principle, the need to conduct thorough screening in patients coming from geographical areas or hospitals where an infection of *C. auris* was described becomes fundamental.

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