Ad Hoc Infectious Disease Forum

Global Epidemiology of *Candida auris*

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衞生防護中心
Centre for Health Protection

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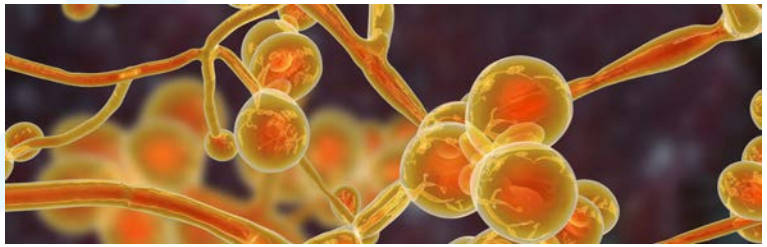
Department of Health

Declaration of interest

- There is no personal or financial interest to declare for this presentation

About *Candida auris*

- First reported in 2009 as a novel yeast isolated from the external ear canal of a 70-year-old woman in a Japanese hospital
- Public health problem because:
  - Multi-drug resistance
  - Ability to cause severe disease
  - Difficulties with laboratory detection
  - Becoming more common
  - Propensity to cause outbreaks in hospitals and nursing homes



CDC

- CDC issued clinical alert to US healthcare facilities in June 2016 (https://www.cdc.gov/fungal/candida-auris/candida-auris-alert.html)

Transmission

- Transmission
  - Exact mode of transmission yet to be identified
  - Early evidence suggested exposure to contaminated facilities / from healthcare personnel / hand transmission / contamination of surfaces

"C. auris colonized patients can have very high burden on their skin (often exceeded 10^6-10^7 cells/mL). This bioburden is positively correlated with the *C. auris* concentrations on associated surfaces. These findings support the shedding hypothesis and provide a new perspective to focus infection control efforts."

J. Sexton, et al. **Mechanisms of *Candida auris* Transmission within the Healthcare Environment.** Abstract presented at ASM Microbe 2019

Clinical presentation

- Asymptomatic colonization: skin, ENT, urine, indwelling devices
- Clinical manifestation depends upon the site of infection
  - Invasive: Bloodstream infection / intraabdominal candidiasis
  - Non-invasive: Can also cause wound infections and otitis
- Infections caused by *C. auris* no different from those caused by other types of *Candida* but can be more difficult to treat
- Crude in-hospital mortality rate 30-72%
- Affects both paediatrics and adults, and has predominantly been identified in critically unwell patients in high dependency settings.

Source: CDC, State Government of Victoria, Australia, Public Health England
Cortegiani et al. Journal of Intensive Care (2018) 6:69

Risk factors for infection

- Nursing home exposure / prolonged hospital stay
- Invasive devices
  - Tracheostomy tubes
  - Percutaneous endoscopic gastrostomy tubes
- Immunocompromised
- Use of broad-spectrum antimicrobial drugs

1) Park J, et al. Management of Patients with Candida auris Fungemia at Community Hospital, Brooklyn, New York, USA, 2016–2018. Emerg Infect Dis. 2019;25(3):601-602.
2) https://www2.health.vic.gov.au/public-health/infectious-diseases/disease-information-advice/candida-auris

Volume 23, Number 2—February 2017

Dispatch

Biofilm-Forming Capability of Highly Virulent, Multidrug-Resistant *Candida auris*

Leighann Sherry, Gordon Ramage, Ryan Kean, Andrew Borman, Elizabeth M. Johnson, Malcolm D. Richardson, and Riina Rautemaa-Richardson

Author affiliations: University of Glasgow, Glasgow, Scotland, UK (L. Sherry, G. Ramage, R. Kean); Public Health England, Bristol, UK (A. Borman, E.M. University of Manchester, Manchester, UK (M.D. Richardson, R. Rautemaa-Richardson); University Hospital of South Manchester, Manchester (M.D. Rautemaa-Richardson)

Main Article

Sherry L, et al. Emerg Infect Dis. 2017 Feb;23(2):328-331. doi: 10.3201/eid2302.161320.

Figure 1

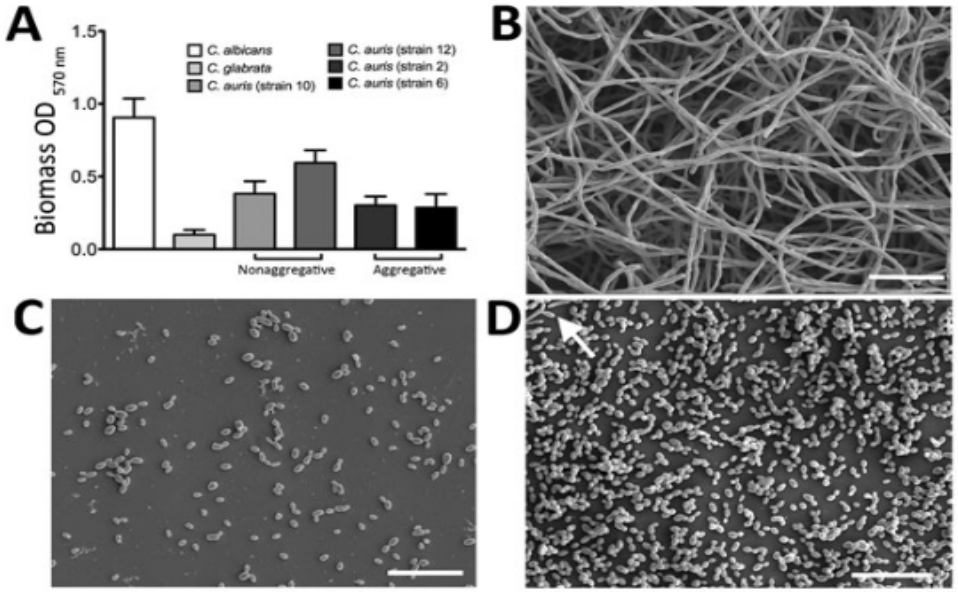


Figure 1. Biofilm formation on *Candida auris*, *C. albicans*, and *C. glabrata* yeast strains. A) Biomass quantities were determined spectrophotometrically for 4 strains of *C. auris* and 1 each of Isolates were standardized to 10^6 cells/mL in RPMI-1640 and grown in flat-bottomed 96-well microtiter plates for 24 h at 37°C. Biofilms were then washed, stained with crystal violet solutio represent the mean ± SD of experiments performed on 3 separate occasions, using 8 replicates for each strain. Results show that *C. auris* can form heterogeneous intermediate biofilms. B (C) and *C. auris* (D) were also grown on Thermanox coverslips (Thermo Fisher Scientific, Paisley, UK) for 24 h at 37°C. Biofilms were then processed and viewed on a JEOL (Tokyo, Japan) JSM- microscope; images were assembled using Photoshop software (http://www.photoshop.com/products). Arrow indicates pseudohyphae in *C. auris* biofilm (D). Scale bars represent 20 μm (c OD, optical density.

Antifungal resistance profile of *C. auris*

- Commonly multidrug resistant but vary widely across isolates
- In the United States
  - About 90% isolates have been resistant to fluconazole
  - About 30% have been resistant to amphotericin B
  - <5% have been resistant to echinocandins (but resistance can arise during treatment & need close monitoring)
- Some isolates have been found to be resistant to all three classes of antifungal drugs - 2 US cases pan-resistance to treatment
- Resistance to triazole antifungal agents
  - Fluconazole resistance may be due to mutation in the Erg11 gene
  - Isolates resistant to fluconazole may respond to other triazoles occasionally (e.g. Voriconazole and other 2nd generation triazoles)

https://www.cdc.gov/fungal/candida-auris/c-auris-antifungal.html

Cortegiani et al. Journal of Intensive Care (2018) 6:69

Resistance to antifungal agents

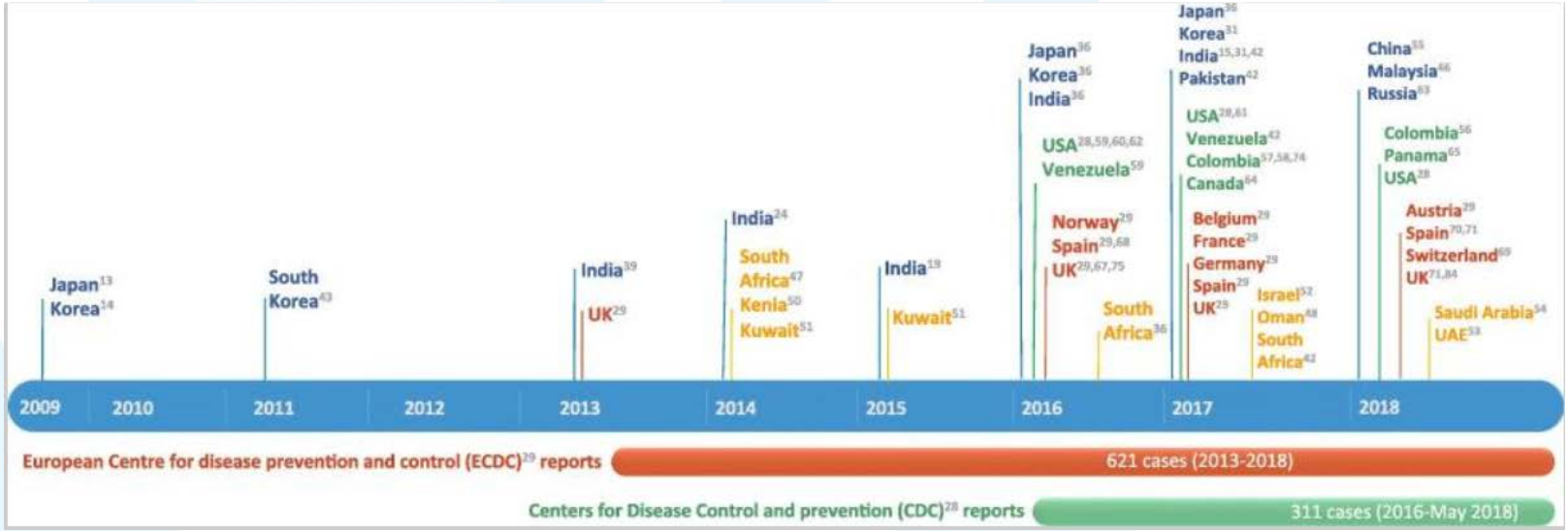
Minimum inhibitory concentration (MIC) range and tentative MIC breakpoints of *C. auris* for most common antifungal drugs. Data retrieved by Centers of Disease Control and Prevention (CDC) website—https://www.cdc.gov/fungal/candida-auris/recommendations.html

Drugs	MIC range (mcg/ml)	Tentative MIC breakpoints (mcg/ml)
Triazoles		
Fluconazole	0.12 to > 64	≥ 32
Voriconazole (and other 2° generation azoles)	0.032–16	N/A
Polyenes		
Amphotericine B	0.06–8	≥ 2
Echinocandins		
Anidulafungin	0.015–16	≥ 4
Caspofungin	0.03–16	≥ 2
Micafungin	0.015–8	≥ 4

Source: Andrea Cortegiani et al. Epidemiology, clinical characteristics, resistance, and treatment of infections by Candida auris. J Intensive Care. 2018; 6: 69 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6206635/

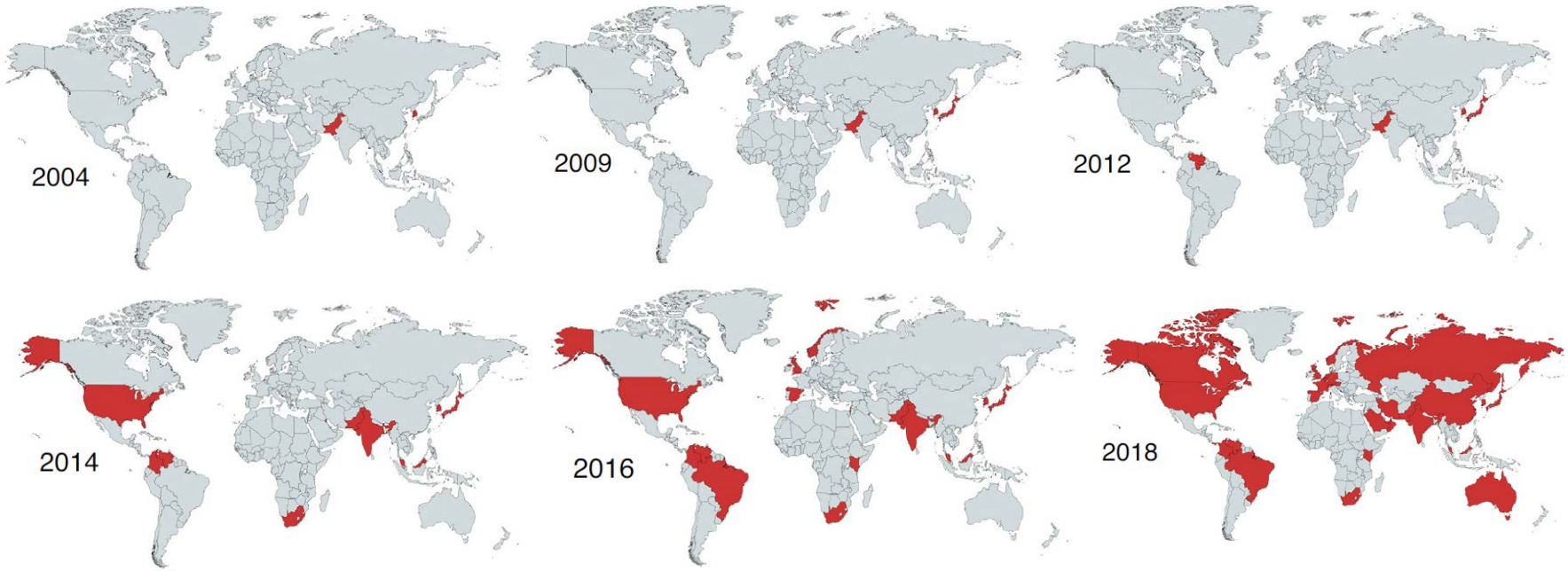
Overseas situation

- First identified in 2009 at a geriatric hospital in Japan and then as nosocomial fungemia in Korea in 2011
- Retrospective identification by DNA sequencing revealed the earliest known strain of *C. auris* was from a bloodstream isolate in 1996 in a paediatric surgery patient in Korea, and another in 2008 in Pakistan.



Source: Andrea Cortegiani et al. Epidemiology, clinical characteristics, resistance, and treatment of infections by Candida auris. J Intensive Care. 2018; 6: 69
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6206635/

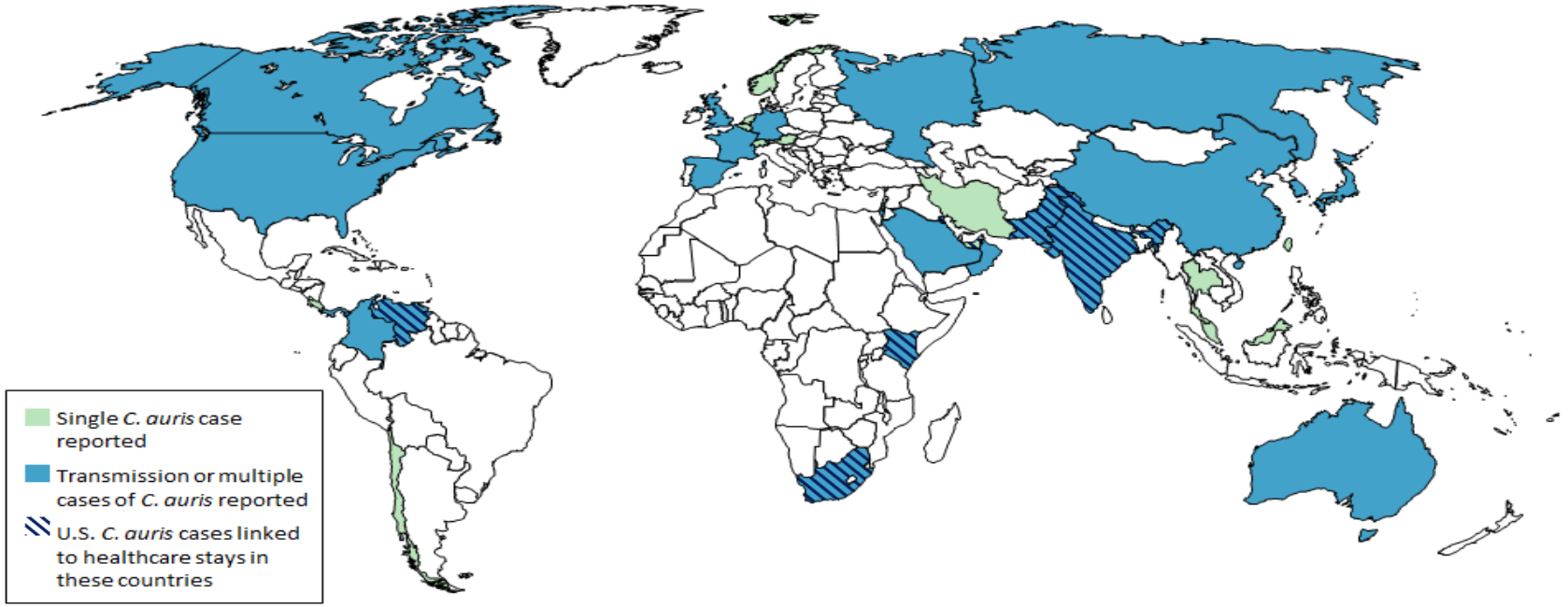
Global situation from 2004 to 2018



Source: Johanna Rhodes and Matthew C Fisher. Global epidemiology of emerging *Candida auris*. Current Opinion in Microbiology. Volume 52, December 2019, Pages 84-89

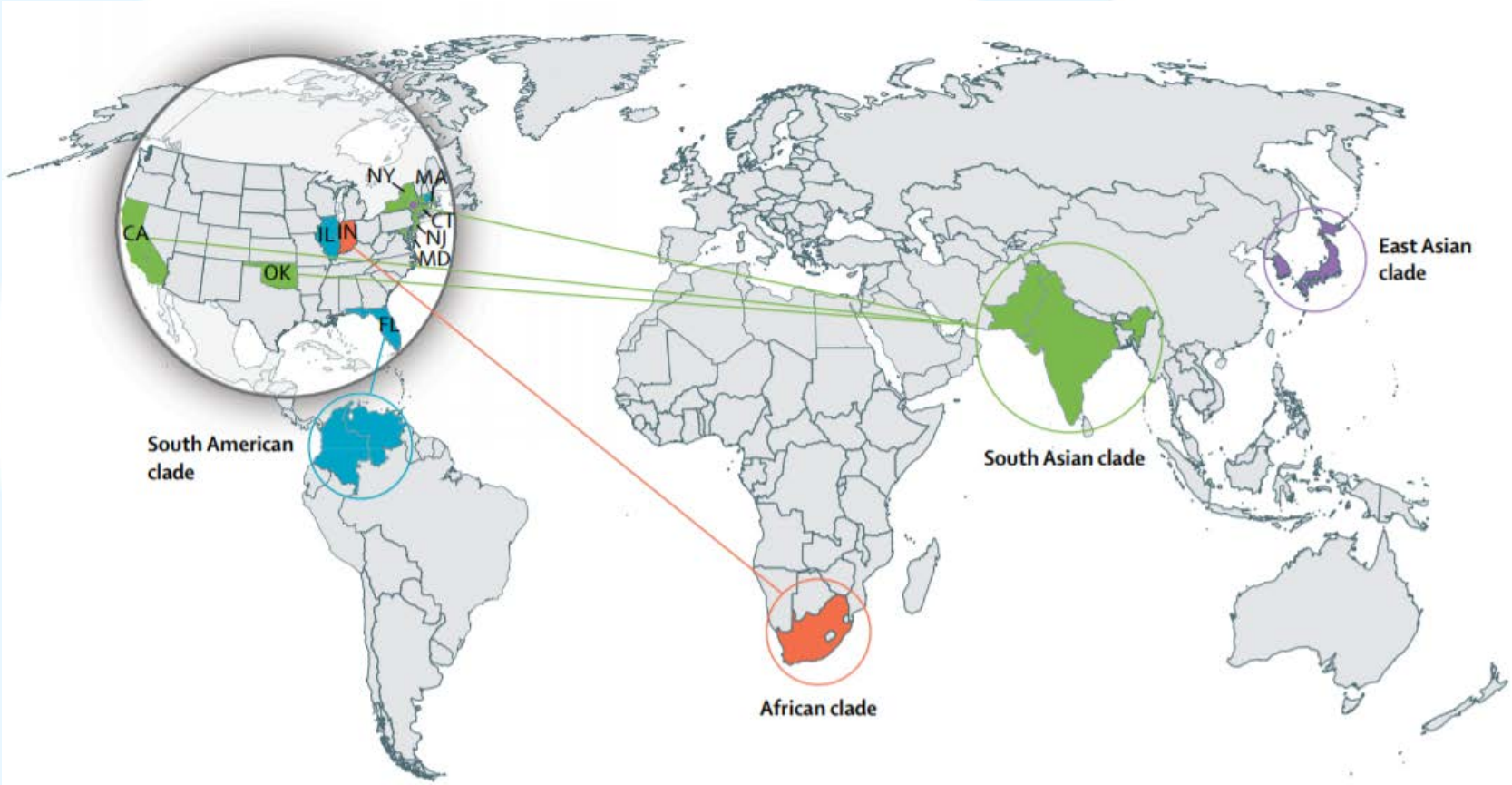
Global situation as at 31 May 2019

Countries from which *Candida auris* cases have been reported, as of May 31, 2019



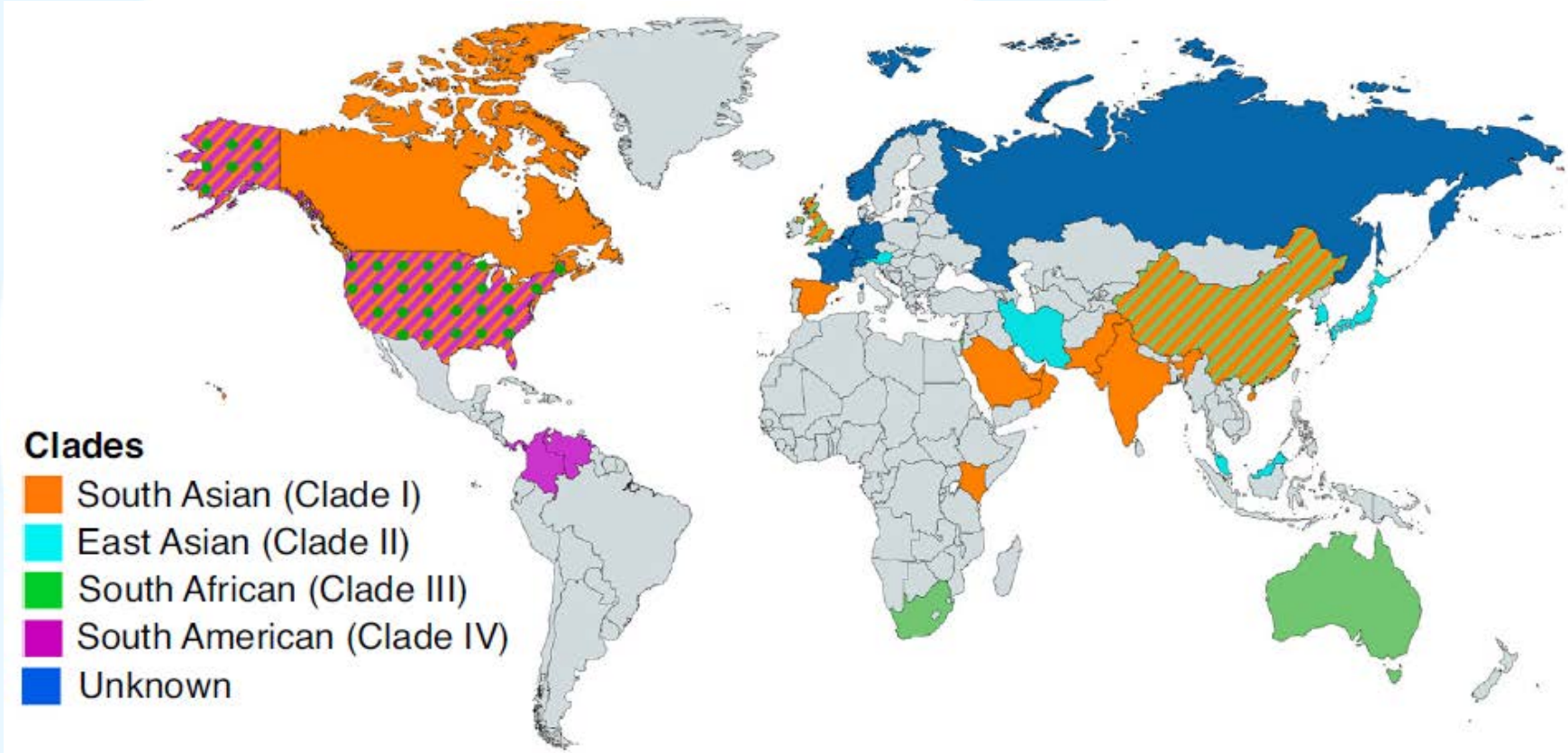
- Single cases of *C. auris* have been reported from Austria, Belgium, Chile, Costa Rica, Iran, Malaysia, the Netherlands, Norway, Switzerland, Taiwan, Thailand, and the United Arab Emirates.
- Multiple cases of *C. auris* have been reported from Australia, Canada, China, Colombia, France, Germany, India, Israel, Japan, Kenya, Kuwait, Oman, Pakistan, Panama, Russia, Saudi Arabia, Singapore, South Africa, South Korea, Spain, the United Kingdom, the United States (primarily from the New York City area, New Jersey, and the Chicago area) and Venezuela; in some of these countries, extensive transmission of *C. auris* has been documented in more than one hospital.

4 major clades of *C. auris* identified in US (11 May 2013 - 31 Aug 2017)



Chow NA et al. Multiple introductions and subsequent transmission of multidrug-resistant Candida auris in the USA: a molecular epidemiological survey. Lancet Infect Dis. 2018 Dec;18(12):1377-1384.

Global distribution of *C. auris clades* (As of 28 February 2019)



Johanna Rhodes and Matthew C Fisher. Global epidemiology of emerging *Candida auris*. Current Opinion in Microbiology. Volume 52, December 2019, Pages 84-89

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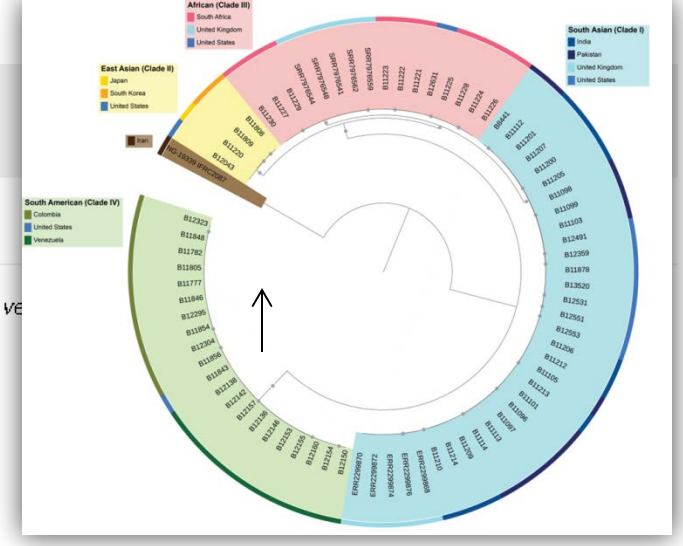


Volume 25, Number 9—September 2019

Research Letter

Potential Fifth Clade of *Candida auris*, Iran, 2018

Nancy A. Chow, Theun de Groot, Hamid Badali, Mahdi Abastabar, Tom M. Chiller, and Jacques F. Meis

Author affiliations: Centers for Disease Control and Prevention, Atlanta, Georgia, USA (N.A. Chow, T.M. Chiller); Canisius Wilhelmina Hospital, Nijmegen, the Netherlands (T. de Groot, J.F. Meis); Mazandaran University of Medical Sciences, Sari, Iran (H. Badali, M. Abastabar)

Suggested citation for this article

Abstract

Four major clades of *Candida auris* have been described, and all infections have clustered in these 4 clades. We identified an isolate representative of a potential fifth clade, separated from the other clades by >200,000 single-nucleotide polymorphisms, in a patient in Iran who had never traveled outside the country.

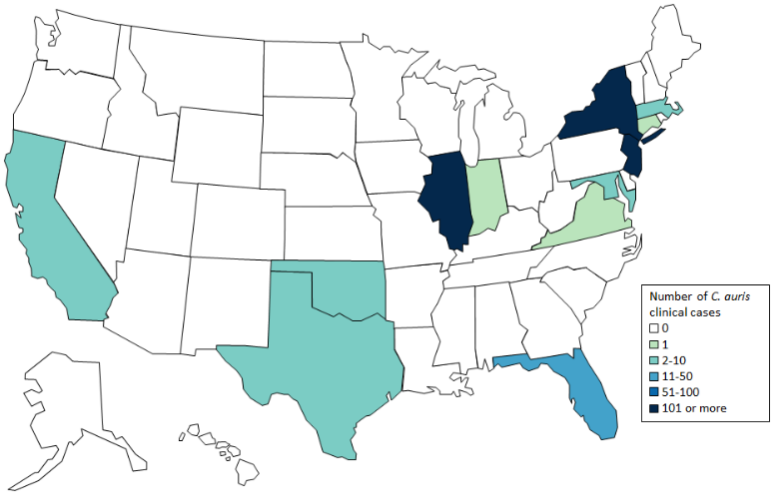
In the last decade, *Candida auris* has emerged in healthcare facilities as a multidrug-resistant pathogen that can cause outbreaks of invasive infections (*1*). *C. auris* has now been identified in >35 countries, many of which have documented healthcare-associated person-to-person spread (*2*). Transmission of this yeast is facilitated by its ability to colonize skin and other body sites, as well as its ability to persist for weeks on surfaces and equipment (*3*).

Chow NA, de Groot T, Badali H, Abastabar M, Chiller TM, Meis JF. Potential fifth clade of *Candida auris*, Iran, 2018. Emerg Infect Dis. 2019 Sep

C. auris as a notifiable disease in the US

- Notifiable nationally
- As at 31 May 2019
  - 685 confirmed clinical cases
  - 30 probable clinical cases
  - 1341 colonized/screening cases
- Most cases have been detected in New York, New Jersey, Illinois, Florida, California, Texas

U.S. Map: Clinical cases of *Candida auris* reported by U.S. states, as of May 31, 2019



Cases are categorized by the state where the specimen was collected. Most probable cases were identified when laboratories with current cases of *C. auris* reviewed past microbiology records for *C. auris*. Isolates were not available for confirmation. Early detection of *C. auris* is essential for containing its spread in healthcare facilities.

- Predominantly identified among patients with extensive exposure to ventilator units at skilled nursing facilities and long-term acute care hospitals, and those who have received healthcare in countries with extensive *C. auris* transmission

Source: CDC

C. auris in Europe

- Survey to national focus points for collaboration with ECDC revealed > 600 cases of *C. auris* detection in EU/EEA
- 620 cases were reported between 2013 and 2017
  - Spain (n = 388), the UK (n = 221), Germany (n = 7), France (n = 2), Belgium (n = 1) and Norway (n = 1)
  - Austria detected 1 case in January 2018
- *C. auris* is detected with increasing frequency and large outbreaks have occurred in Europe since 2013.
- Adequate laboratory capacity, surveillance, and infection control preparedness is required in all EU/EEA countries.

Kohlenberg Anke, et al. The Candida auris survey collaborative group. Candida auris: epidemiological situation, laboratory capacity and preparedness in European Union and European Economic Area countries, 2013 to 2017. Euro Surveill. 2018;23(13)

C. auris in Europe

Number of *Candida auris* cases detected in the European Union/European Economic Area, 2013–2017 (n = 620)[a]

Year	*Candida auris* bloodstream infection		Other type of *C. auris* infection		*C. auris* colonisation		Cases of unknown infection/ colonisation status		Total
	n	%	n	%	n	%	n	%	n
2013	1	33.3	0	0.0	0	0.0	2	66.7	3
2014	0	0.0	1	100.0	0	0.0	0	0.0	1
2015	6	26.1	11	47.8	6	26.1	0	0.0	23
2016	53	18.3	13	4.5	223	76.9	1	0.3	290
2017	50	16.5	15	5.0	237	78.2	1	0.3	303
2013–2017	110	17.7	40	6.5	466	75.2	4	0.6	620

All percentages are row percentages.

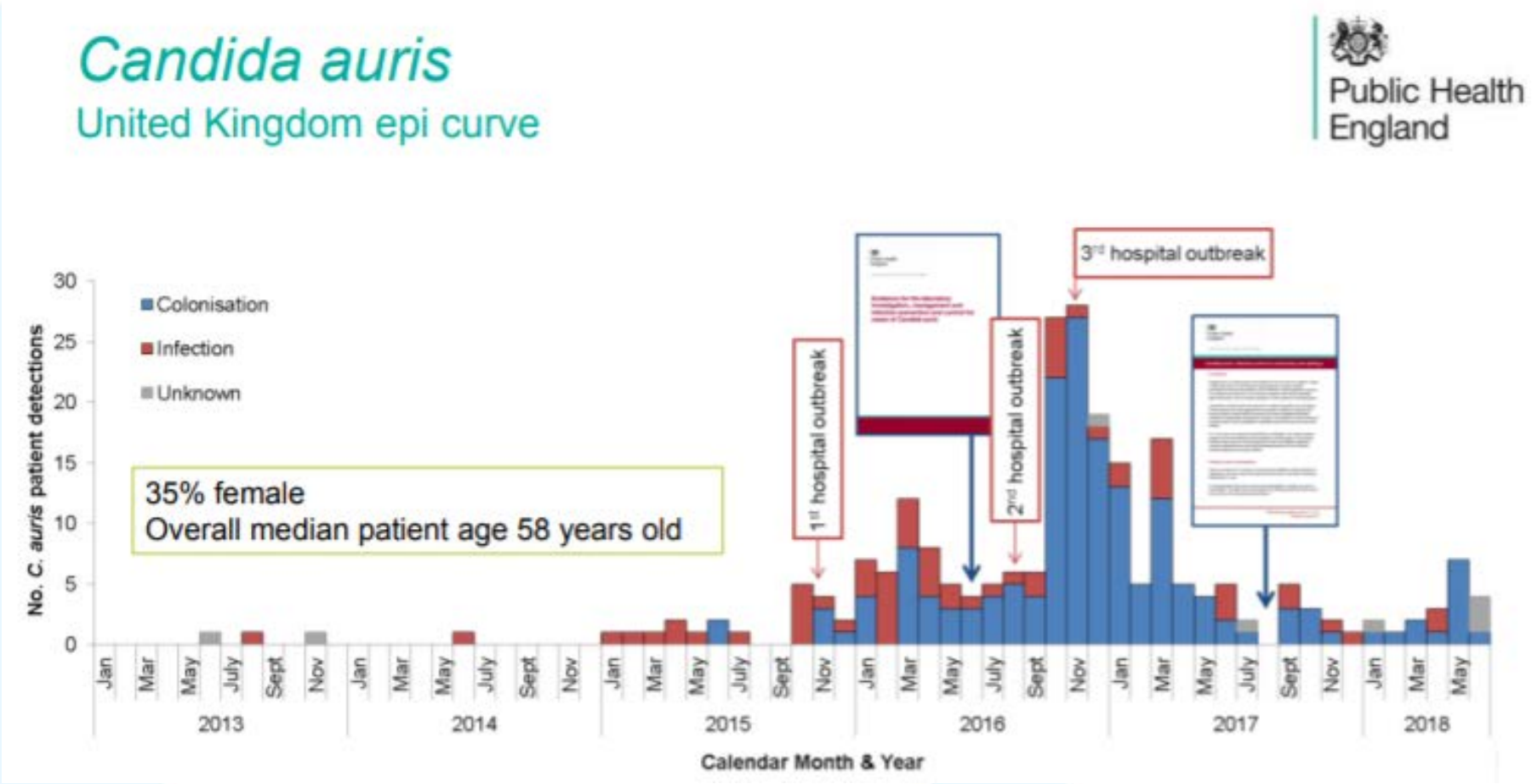
[a] One additional case detected in Austria in January 2018 is not included in the table.

C. auris in the UK

- As at the beginning of July 2017, 20 separate NHS Trusts and independent hospitals in the UK had detected >200 patients colonised or infected.
  - Three hospitals have seen large nosocomial outbreaks that have proved difficult to control, despite intensive infection prevention and control measures
  - >35 other hospitals had patients colonised with *C. auris*
- Most detections from colonised patients, picked up through enhanced surveillance activities in the 3 most affected hospitals.
- About 25% detections associated with clinical infections (27 patients with developed blood stream infections)
- No attributable mortality to *C. auris* within the UK (all-cause 30-day mortality ~20%), in contrast to the high case fatality reported in the literature

Candida auris within the United Kingdom: updated guidance published Public Health England. Updated 11 August 2017

C. auris in the UK



Source: Public Health England

C. auris in the UK

- One of the hospital outbreaks affecting 70 patients linked to reusable axillary temperature probes, indicating that this emerging pathogen can persist in the environment and be transmitted in health care settings

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A *Candida auris* Outbreak and Its Control in an Intensive Care Setting

David W. Eyre, D.Phil., Anna E. Sheppard, Ph.D., Hilary Madder, F.A.N.Z.C.A., Ian Moir, Ruth Moroney, M.Sc., T. Phuong Quan, M.Sc., David Griffiths, B.Sc., Sophie George, M.Sc., Lisa Butcher, M.Sc., Marcus Morgan, M.Sc., Robert Newnham, Mary Sunderland, B.Sc., Tiphanie Clarke, B.A., Dona Foster, Ph.D., Peter Hoffman, B.Sc., Andrew M. Borman, Ph.D., Elizabeth M. Johnson, Ph.D., Ginny Moore, Ph.D., Colin S. Brown, F.R.C.Path., A. Sarah Walker, Ph.D., Tim E.A. Peto, F.R.C.P., Derrick W. Crook, F.R.C.Path., and Katie J.M. Jeffery, Ph.D.

N Engl J Med 2018; 379:1322-1331

C. auris in Spain

- An outbreak between April 2016 and January 2017
  - 140 patients with +ve cultures, including 41 candidaemia patients
  - All isolates resistant to fluconazole & voriconazole but susceptible to echinocandin and amphotericin B
  - 30-day mortality rate for those with candidiaemia: 41.4%

Received: 30 March 2018 | Accepted: 3 April 2018
DOI: 10.1111/myc.12781

ORIGINAL ARTICLE

WILEY mycoses

An outbreak due to *Candida auris* with prolonged colonisation and candidaemia in a tertiary care European hospital

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[9]Centre of Expertise in Mycology

Summary

Multidrug-resistant *Candida auris* has emerged as a cause of insidious hospital outbreaks and complicated infections. We present the analysis of an ongoing *C. auris* outbreak including the largest published series of *C. auris* bloodstream infection. All *C. auris*-positive patients from April-2016 to January-2017 were included. Environmental, clinical and microbiological data were recorded. Definitive isolate identification was performed by ITS-rDNA sequencing, and typing by amplified fragment length polymorphism fingerprinting. One hundred and forty patients were colonised by *C. auris* during the studied period (68% from surgical intensive care). Although control measures were implemented, we were not able to control the outbreak. Forty-one invasive bloodstream infections (87.8% from surgical intensive care) were included. Clinical management included prompt intravascular catheter removal and antifungal therapy with echinocandins. All isolates were fluconazole- and voriconazole-resistant, but echinocandin- and amphotericin B-susceptible. Thirty-day mortality rate was 41.4%, and severe septic metastasis as spondylodiscitis and endocarditis were observed in 5 patients (12%). *C. auris* was also recovered from inanimate patient surroundings and medical equipment. Despite antifungal treatment,

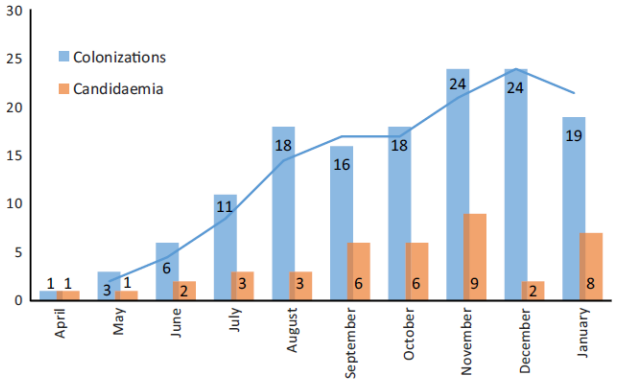

FIGURE 1 Epidemic curve of candidaemia episodes (n = 41) and new colonised patients (n = 140) by *Candida auris* from April 2016 to January 2017

衛生防護中心 Centre for Health Protection

C. auris in Asia

Emergence of multidrug-resistant *Candida auris* in Taiwan

Taiwan

Sir,

Candida auris has been declared an emerging multidrug-resistant yeast and poses a great challenge in the field of infection control and prevention [1,2].

A 55-year-old man with a medical history of diabetes mellitus and pemphigus vulgaris underwent treatment with azathioprine (50 mg/day) and prednisolone (5 mg/day). Between 9 November 2017 and 30 December 2017 he was hospitalised at Chi Mei Medical Center (CMMC), located in Tainan City, Taiwan, due to pemphigus vulgaris-related skin and soft-tissue infection caused by methicillin-resistant *Staphylococcus aureus* (MRSA), where he received anti-MRSA treatment. On 11 April 2018, several ruptured vesicles with erythematous changes and purulent discharge over the face were noted. The patient was a resident in Tainan City and did not have any overseas travel history prior to the hospital visit on 11 April 2018.

Bacterial cultures were obtained from the ruptured vesicles over the face and *Candida* sp. along with MRSA were recovered from trypticase soy agar plates supplemented with 5% sheep blood (Becton Dickinson & Co., Sparks, MD). Oral fluconazole (200 mg/day), in addition to minocycline, was prescribed for 14 days. Identification of the *Candida* sp. by matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF/MS) (Bruker Biotyper MS; Bruker Daltonik GmbH, Bremen, Germany) from the growth on blood agar plates by the direct smear method yielded *C. auris* (score value, 1.857). Oral posaconazole (100 mg/day) was administered for 7 days. A follow-up fungal

International Journal of Antimicrobial Agents 53 (2019) 705–706

7TH MAY 2019 Singapore

Name and Constituency of Member of Parliament
Dr Chia Shi-Lu
MP for Tanjong Pagar GRC

Candida auris is one example of an antimicrobial resistant fungus. It was first identified in 2009 in Japan and subsequently reported from other parts of the world, including Singapore. The first case of Candida auris here was reported in 2012. To date, a total of 16 cases have been detected in the public and private hospitals. Investigations showed that the cases are unlinked, and there is no report of local spread.

https://www.moh.gov.sg/news-highlights/details/preventive-measures-at-hospitals-in-light-of-emergence-of-drug-resistant-superbugs/

Emergency of fungemia cases caused by fluconazole-resistant *Candida auris* in Beijing, China

The first isolate of *C. auris* from China was reported in 2018 after isolation from the bronchoalveolar lavage fluid of a hospitalized woman.[7] This isolate is susceptible to all tested antifungals including amphotericin B, fluconazole, and caspofungin. Recently, 15 cases of fluconazole-resistant *C. auris* were identified in intensive care units of a hospital in Shenyang, which is located in Northwest China.[8] The isolates were mainly associated with urinary tract infections. Here, we report two cases of fungemia caused by fluconazole resistant *C. auris* in Beijing. This study was approved by the institutional ethics committees of The Army General Hospital, Beijing, China. As all the data were collected and analyzed anonymously, the requirement for informed consent was waived.

On June 5, 2018, two *C. haemulonii* isolates (C1921 and C1922)

Journal of Infection 77 (2018) 561–571

衛生防護中心 Centre for Health Protection

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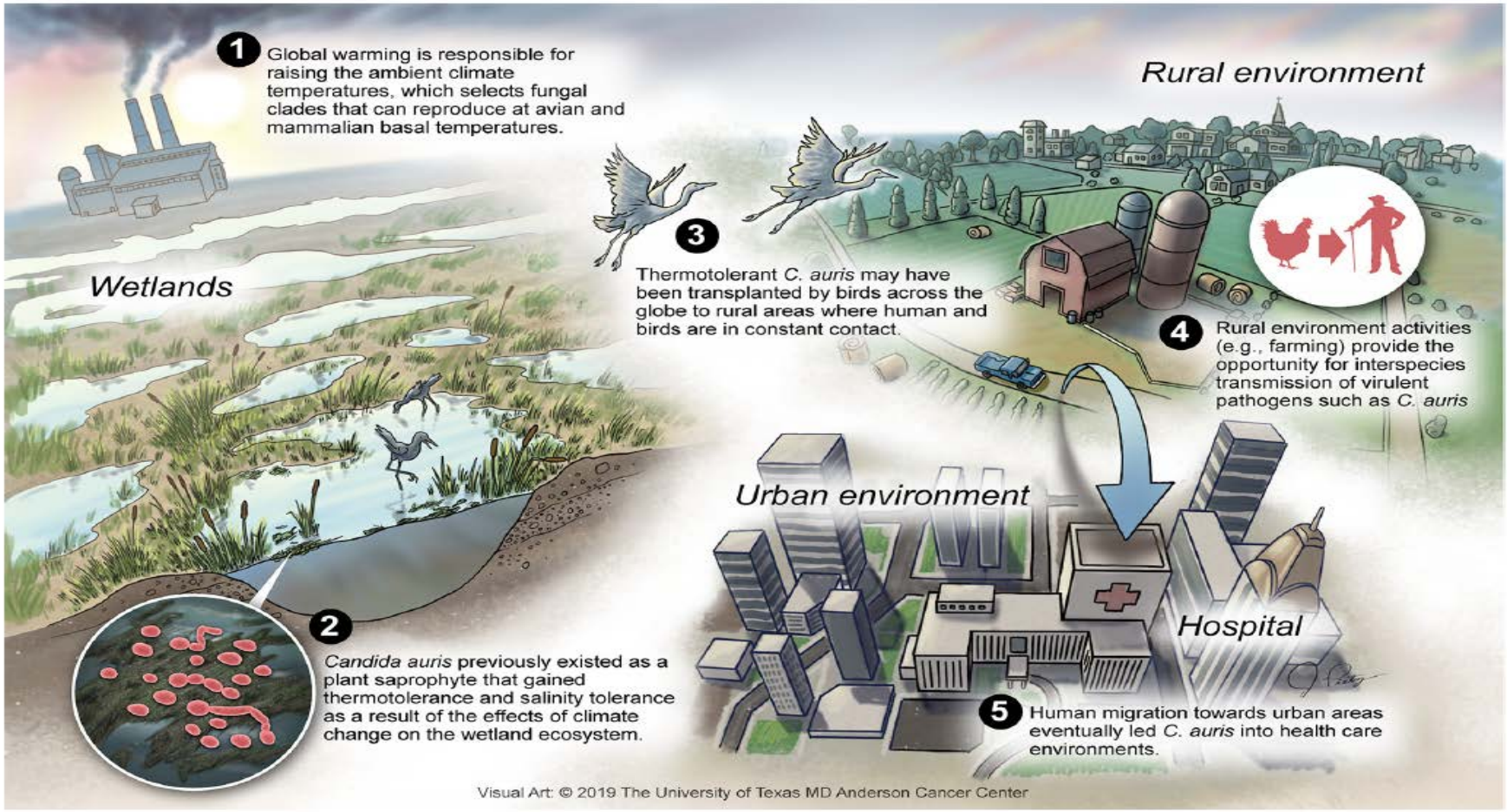
C. auris in South Korea

ABSTRACT *Candida auris* is an emerging worldwide fungal pathogen. Over the past 20 years, 61 patient isolates of *C. auris* (4 blood and 57 ear) have been obtained from 13 hospitals in Korea. Here, we reanalyzed those molecularly identified isolates using two matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) systems, including Biotyper and Vitek MS, followed by antifungal susceptibility testing, sequencing of the *ERG11* gene, and genotyping. With a research-use-only (RUO) library, 83.6% and 93.4% of the isolates were correctly identified by Biotyper and Vitek MS, respectively. Using an *in vitro* diagnostic (IVD) library of Vitek MS, 96.7% of the isolates were correctly identified. Fluconazole-resistant isolates made up 62.3% of the isolates, while echinocandin- or multidrug-resistant isolates were not found. Excellent essential (within two dilutions, 96.7%) and categorical agreements (93.4%) between the Clinical and Laboratory Standards Institute (CLSI) and Vitek 2 (AST-YS07 card) methods were observed for fluconazole. Sequencing *ERG11* for all 61 isolates revealed that only 3 fluconazole-resistant isolates showed the Erg11p amino acid substitution K143R. All 61 isolates showed identical multilocus sequence typing (MLST). Pulsed-field gel electrophoresis (PFGE) analyses revealed that both blood and ear isolates had the same or similar patterns. These results show that MALDI-TOF MS and Vitek 2 antifungal susceptibility systems can be reliable diagnostic tools for testing *C. auris* isolates from Korean hospitals. The Erg11p mutation was seldom found among Korean isolates of *C. auris*, and multidrug resistance was not found. Both MLST and PFGE analyses suggest that these isolates are genetically similar.

Kwon YJ, et al 2019. Candida auris clinical isolates from South Korea: identification, antifungal susceptibility, and genotyping. J Clin Microbiol 57:e01624-18.

Emergence of *C. auris* and global warming – a hypothesis



Source: Arturo Casadevall et al. On the Emergence of Candida auris: Climate Change, Azoles, Swamps, and Birds. mBio Jul 2019, 10 (4) e01397-19; DOI: 10.1128/mBio.01397-19

Take Home Messages

- An emerging organism with public health significance
- Propensity to cause nosocomial outbreaks
- Multi-drug resistance
- Ability to cause severe disease
- May have difficulties with laboratory detection

THANK YOU

Special acknowledgement to Dr. KH Kung for help in preparing the presentation