9TH NATIONAL FUNGUS DAY

CANDIDA AURIS: UNRAVELLING THE FUNGAL MENACE

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OBJECTIVES

- Introduction
- Phenotypic CCCs of *C. auris*
- Incidence of *C. auris*
- Virulence factors
- Risk factors
- Antifungal resistance and treatment
- Diagnosis
- Infection control measures

INTRODUCTION

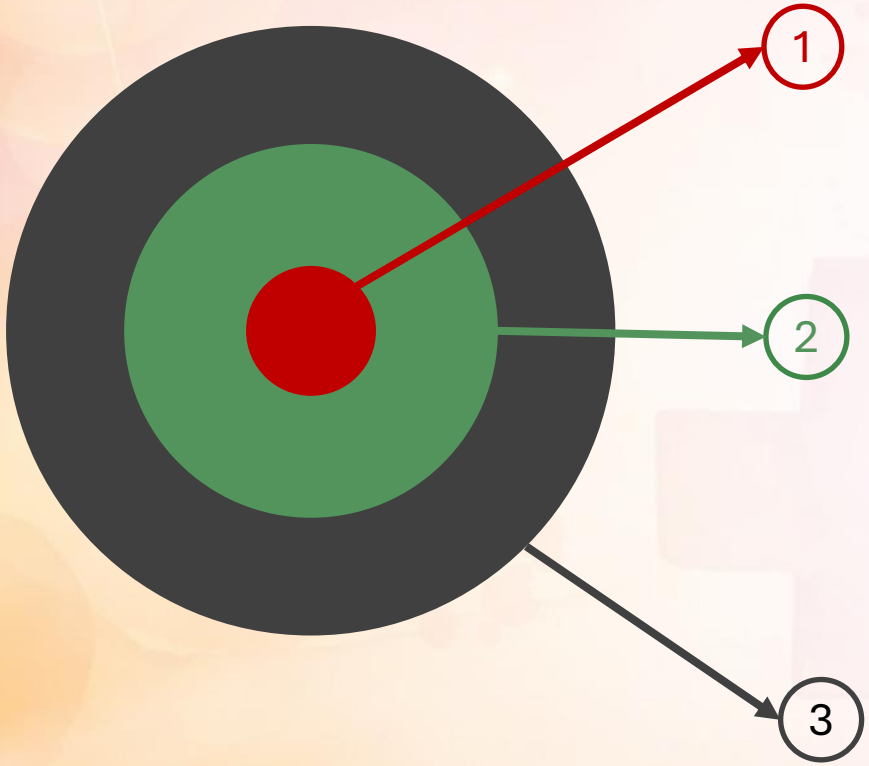
- The incidence of human fungal infections is **increasing at an alarming rate**, as these eukaryotic pathogens currently infect billions of people worldwide and kill more than **1.5 million people per year.**
- **The high mortality rates of invasive fungal infections** are on par with those of common bacterial and parasitic diseases such as ***tuberculosis*** and ***malaria***.
- Approximately 90% of all deaths due to fungal infection are caused by ***Candida***, ***Aspergillus***, or ***Cryptococcus*** species .
- These **three fungal pathogens** are included in **the critical priority group** of the World Health Organization’s recently released list of **fungal priority pathogens** .

INTRODUCTION

- Among these fungal pathogens, ***Candida spp***. are the most significant cause of invasive infections. The associated **mortality rate** ranges from **46%** to **75%,** which has been unchanged for decades.
- The US **Centers for Disease Control and Prevention** classified ***Candida spp***. as a serious threat to human health due to the **dramatic rise in drug-resistant infections**, especially those caused by **non-albicans species.**
- Of particular concern is ***Candida auris* (*C. auris*),** an emerging pathogenic yeast of increasing global concern.

Between 2020 and 2021, *C. auris* cases in U.S. health care facilities rapidly increased, and they continue to be on the rise. The CDC now considers the fungus an urgent antimicrobial resistance threat. In addition, the World Health Organization (WHO) has placed *C. auris* in the critical priority group on its fungal priority pathogens list.

What is *Candida auris*?

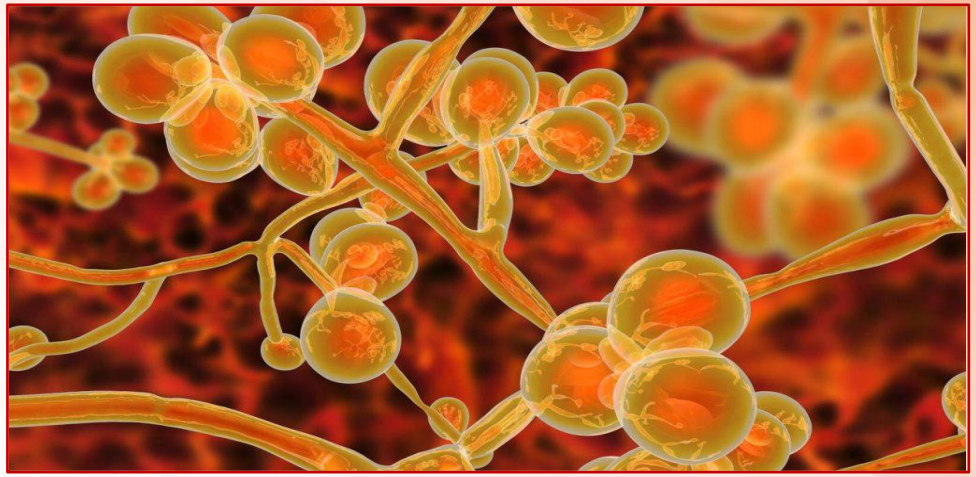


C. auris is an **opportunistic**, **multi-drug resistant pathogen** that continues to spread throughout the world and cause nosocomial outbreaks in both pediatric and adult populations, particularly in intensive care settings.

The pathogen poses a **serious challenge** to healthcare systems due to its **unique features**, including extensive transmission among patients, **persistence** in hospital environments, **misidentification** by traditional laboratory methods, **an antifungal-resistance profile** and an association with **high mortality rates**.

The serious threat that ***C. auris*** poses has prompted public health agencies around the world to **issue alerts** to healthcare facilities on identifying and reporting incidences to health authorities.

Phenotypic Characteristics of ***C. aURIS***



C. auris like other Fungi is a eukaryotic, heterotrophic, mainly aerobic organism, possessing chitin in its cell walls. It is a ubiquitous organism found in association with organic matter.

C. auris differs in many biological aspects from other Candida species. For example, C. auris does not form germ tubes.

C. auris undergoes a phenotypic switch between typical yeast, filamentation-competent yeast, & filamentous cells.

A new chromogenic selective medium, ***CHROMagarTM Candida Plus*** has been developed recently; ***C. auris*** forms pale cream, with a distinctive blue halo and is easily differentiated from other Candida species, including ***C. haemulonii*** .

Emergence of Various Clones of *C. AURIS*

Phylogenetically, ***C. auris*** is closely related to ***C . Haemulonii*** complex members.

Genome-wide single nucleotide polymorphism (SNP)- based phylogenetic analyses have identified **five major clades** across the world: **South Asian (I), East Asian (II), South African (III), South American (IV) and a novel clade from Iran (V).**

A number of clones of ***C. auris*** have emerged in the past decade, in various geographical locations globally .

Until now, nosocomial outbreaks and **invasive infections** have been linked to clades **I, III** and **IV** of ***C. auris***, while **clades II** and **V** have been primarily associated with **ear colonization or infection,** and not with invasive infections.

Clade I has also been associated with increased **antifungal resistance** compared to the other clades of ***C. auris***; this includes a prominent feature of **echinocandin resistance.**

C. AURIS Incidences

C. auris was first isolated from the **external ear canal** of a **Japanese** patient and described as a novel *Candida spp*. In **2009**.

The **first six invasive isolates** were described in **South Korea** in **2011**.

Nosocomial outbreaks, mostly in intensive care settings, were reported across **Europe** and **Africa 2013–2015**, and in **North** and **South America**, starting in **2016**.

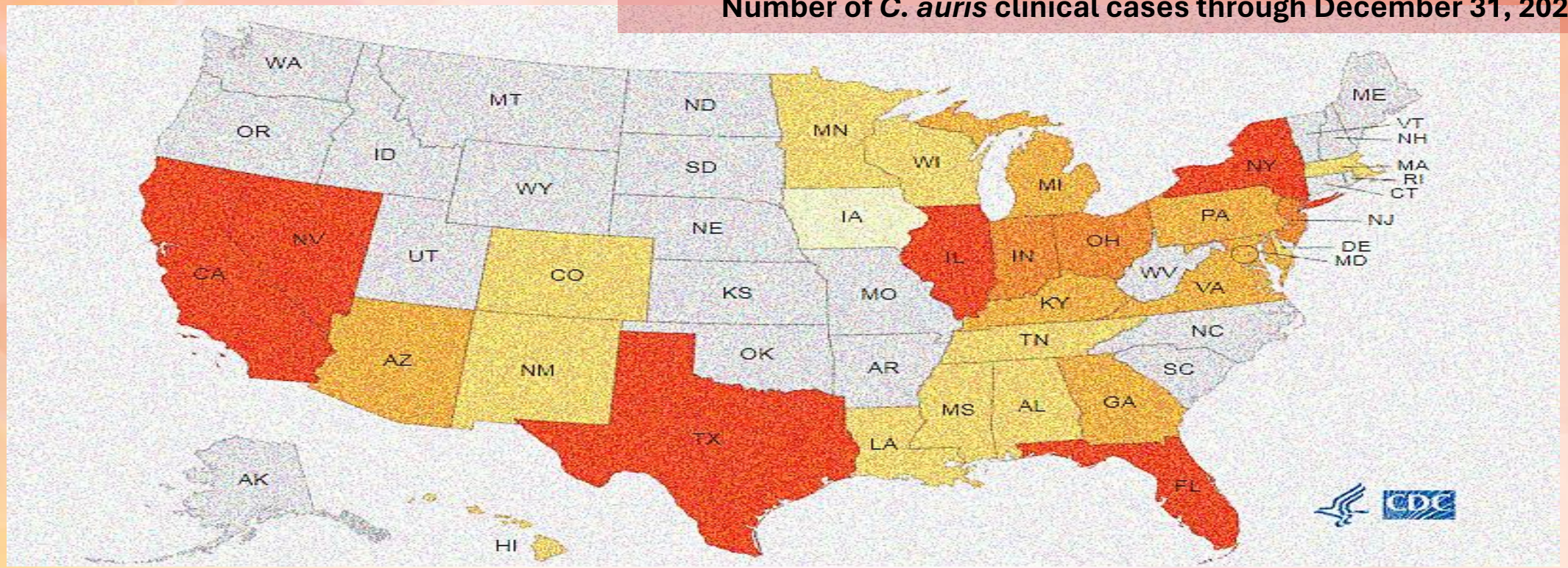
The first incidences of transmission of ***C. auris*** among adults in **Australia** were reported in **2018.**

C. auris has been reported in **six continents** and at least **47 countries.** According to the **European CDC survey**, **10 European countries** have encountered patients **colonized** or **infected** with ***C. auris***.

The emergence of *C. AURIS* in multiple countries

- Several explanations have suggested the emergence of ***C. auris*** in multiple countries.
- One hypothesis is that ***C. auris*** has long been present, but was **not properly recognized** microbiologically and was **misidentified** as a different species.
- Another hypothesis suggests that **increased antifungal use** in healthcare settings and in agriculture exerted selection pressure that favored the emergence of new drug-resistant Candida species.
- An additional plausible explanation relates to the interaction between **global ecological changes** and **increasing mean global temperatures**, and the **distinctive biological properties** of ***C. auris*** compared with other Candida species. These properties include **thermotolerance**, **halotolerance** and the ability to form **resilient aggregates**.

Number of *C. auris* clinical cases through December 31, 2022



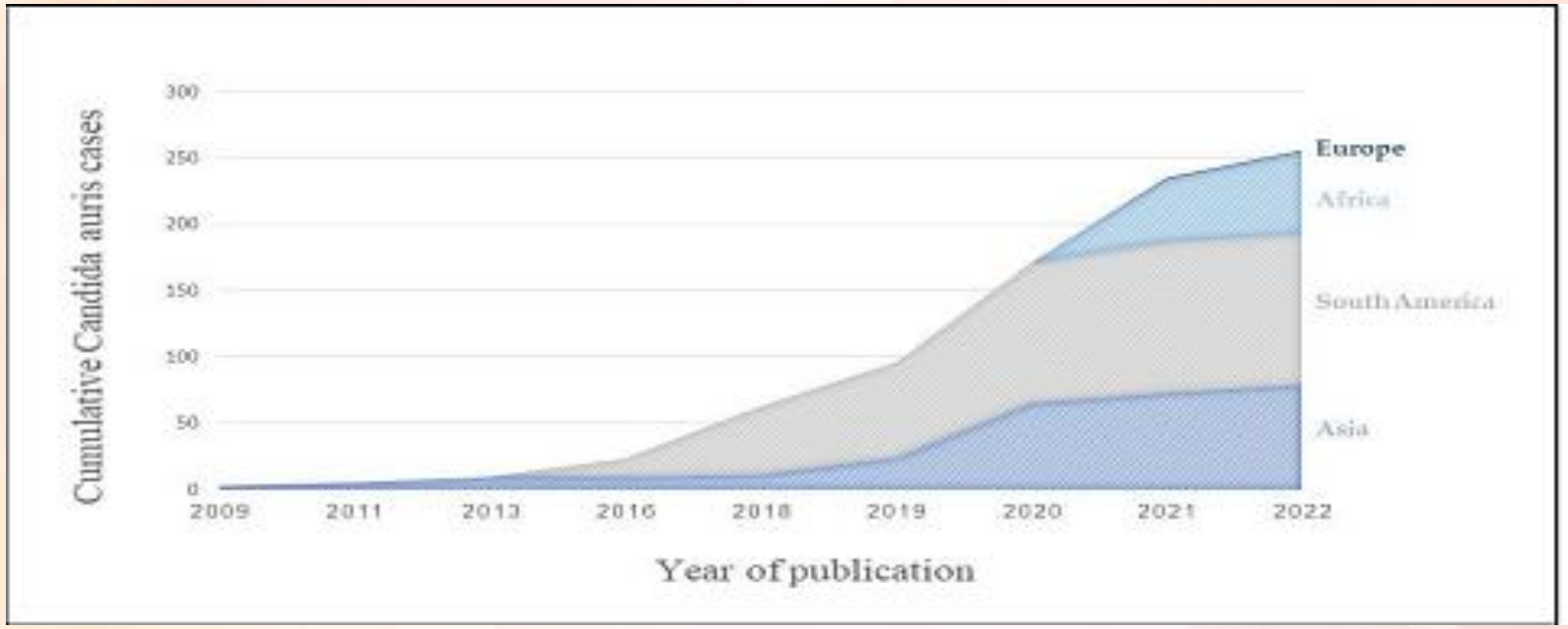
In the most recent 12 months, there were 2,377 clinical cases and 5,754 screening cases (January 2022 - December 2022).

- 0 clincial cases and at least 1 screening case
- 1 to 10
- 11 to 50
- 51 to 100
- 101 to 500
- 501 to 1000
- 1001 or more

Number of patients affected and mortality rates in selected studies reporting outbreaks during January 2019 to January 2021

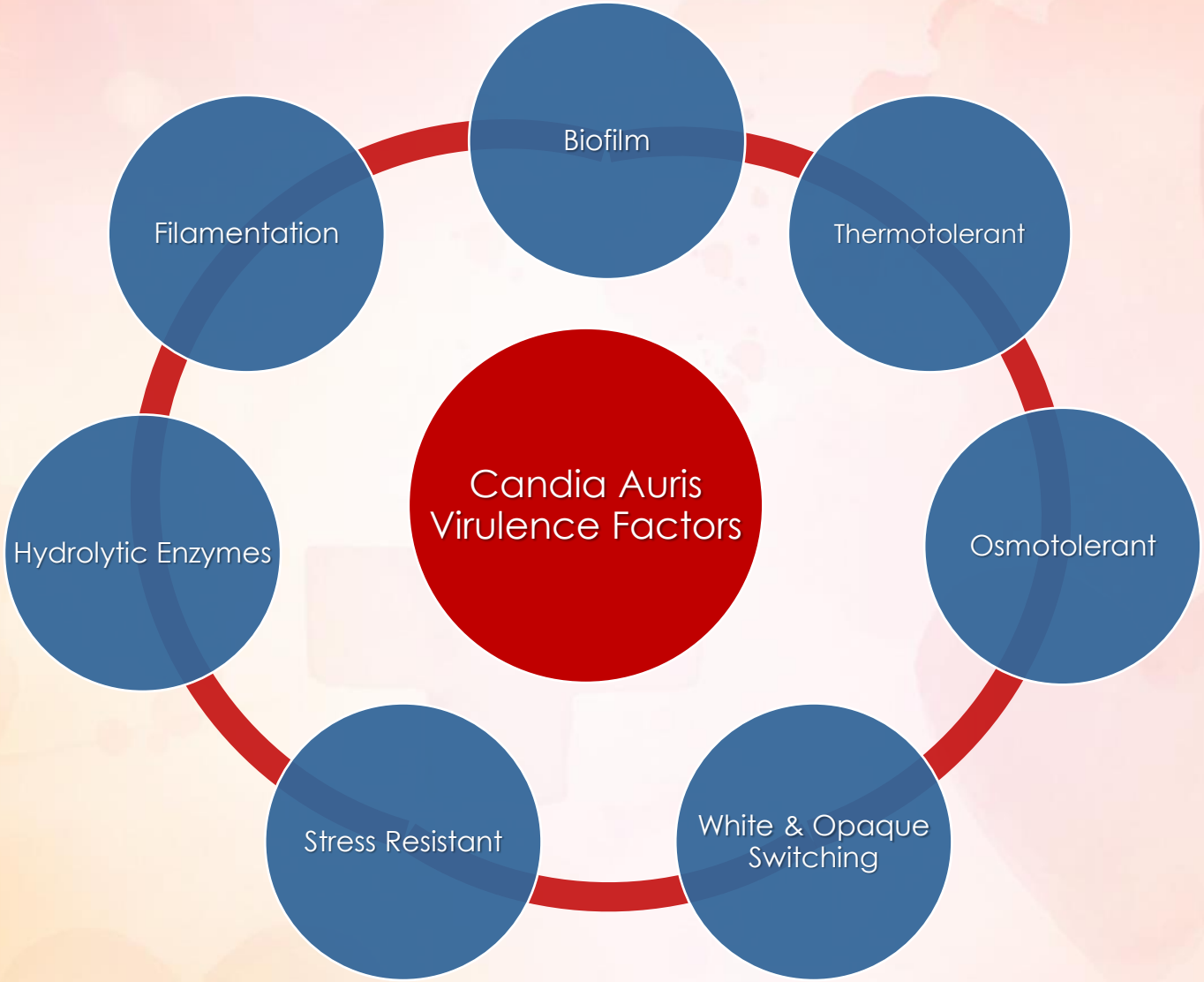
Country	Outbreak Duration	No. of Patients with *C. auris* Causing			Mortality (%)	Reference
		Candidemia	Colonization	Total		
Kuwait	January 2018–June 2019	17	54	71	36 (50.7%)	Alfouzan et al., 2020 [58]
Mexico	April 2020–October 2020	6	6	12	8 (67%)	Villanueva-Lozano et al., 2021 [47]
Oman	April 2018–April 2019	11	21	32	17 (53.1%)	Al-Maani et al., 2019 [56]
Oman	January 2016–December 2019	23	NA	23	9 (39.1%)	Mohsin et al., 2020 [57]
Russia	January 2017–December 2019	38	NA	38	21 (55.3%)	Barantsevich et al., 2020 [54]
Saudi Arabia	March 2018–June 2019	6	29	35	7 (20%)	Alshamrani et al., 2020 [55]
Spain	October 2017–June 2020	47	287	47	11 (23.4%) [a]	Mulet Bayona et al., 2020 [51]
USA	May 2018–April 2019	7	5	12	2 (16.7%)	Arensman et al., 2020 [67]

C. AURIS Incidences in Children



The majority of pediatric incidences were reported from South America (114/256, 45%) and South Asia (67/256, 26%), in several nosocomial outbreaks

C. AURIS Virulence Factors



Insights into the Ecological Niches of ***C. AURIS***

- Although **global warming** and **climate change** are hypothesized to promote the **evolution** of this pathogenic fungus.
- ***C. auris*** has evolved several novel features, including **thermal adaptation** and **saline tolerance**, that mediate its environmental adaptation and survival outside the human host. The **overuse** of **antifungal agents** in both agriculture and human health has contributed to the development of **antifungal resistance** in ***C. auris***.

Clinical Spectrum of *C. AURIS* Infection

The spectrum of *C. auris* infection ranges widely from superficial skin infection to invasive disease such as bloodstream infections. *C. auris* was described as progressing from colonization to invasive infection in 4–25% of affected adults.

C. *auris* has been reported to cause urinary tract infections; otitis and deep-seated infections such as osteomyelitis, myocarditis, wound infections, skin abscesses and meningitis.

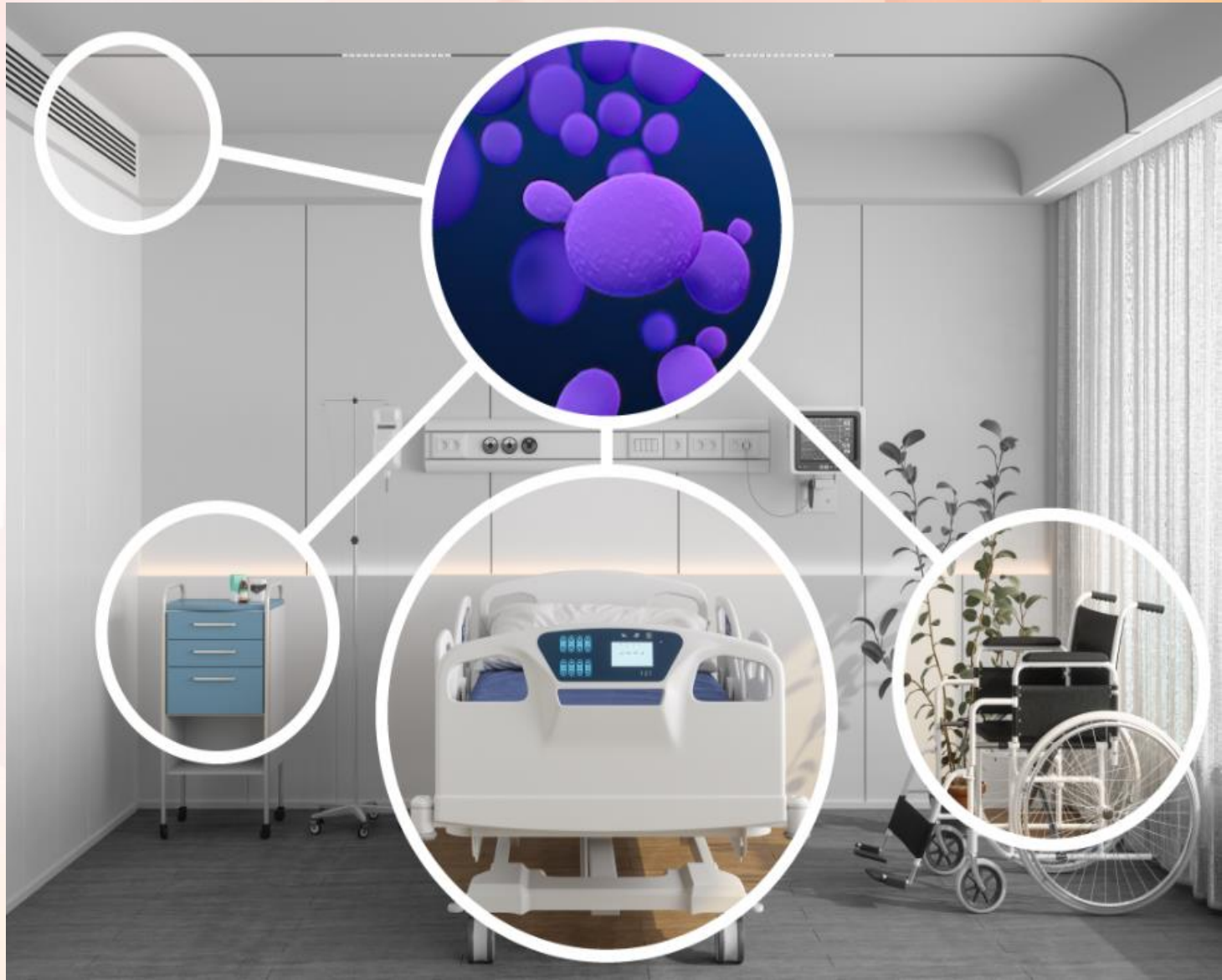
Common sites of *C. auris* colonization described in adults were the skin, especially the groin and axilla areas, and mucosal surfaces, i.e., the genitourinary tract and the gastrointestinal and respiratory tracts (oropharynx, nose, ears).

In children, however, asymptomatic colonization was rarely described. Colonization was reported in a neonate born to a colonized mother; the skin (axilla), eyes and ears were involved . Also, progression from colonization to infection was not clearly described.

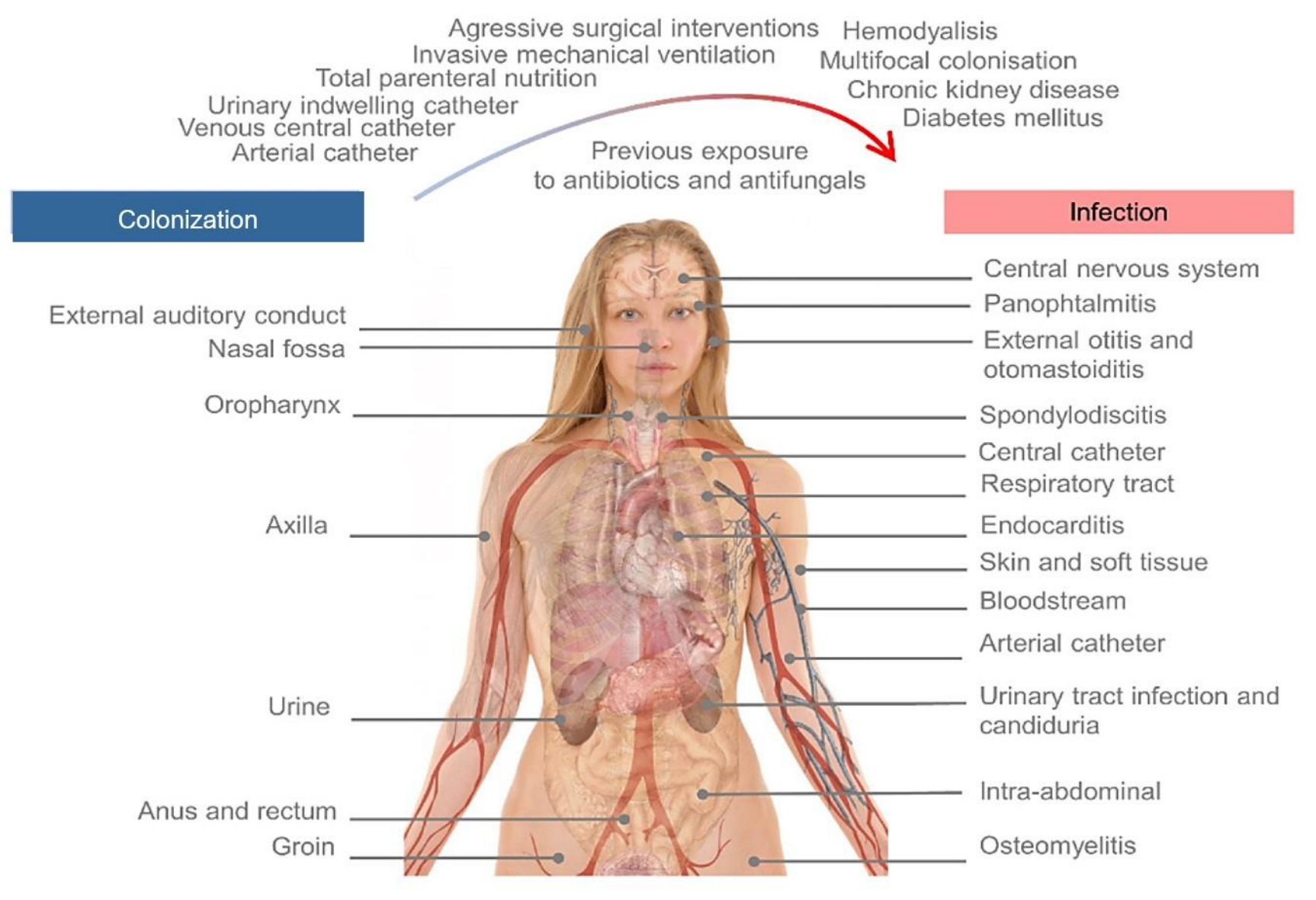
The skin of many nursing-home residents is chronically colonized with C. auris, serving as an important reservoir for its spread. Approximately 30% of colonized residents tested positive at one body site, and 70% were colonized at two or more sites .

How *C. AURIS* is IMPACTING HEALTHCARE FACILITIES?

Contamination of **hospital floors, bed rails, bed-sheets, trolleys, mobile phones, chairs, bed trays, air conditioning units**, and **sink surfaces** with little to no patient contact is also an important factor in ***C. auris*** transmission in health care facilities.



Risk Factors for *C. AURIS* Infection



C. AURIS Microbiologic Identification

Microbiologic identification of ***C. auris*** remains a serious challenge to healthcare systems, especially in developing countries.

However, **early** and **accurate** microbiologic identification of the pathogen is essential for **proper treatment** and **rapid implementation of infection control measures.**

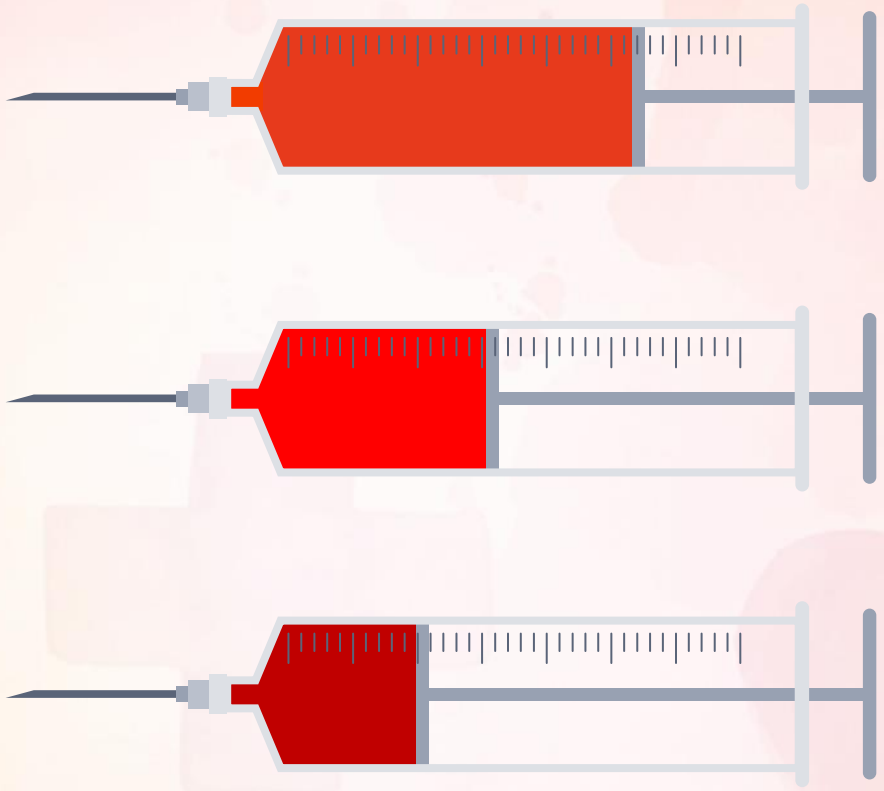
Overall, laboratory capacities to identify ***C. auris*** have advanced considerably; however, not all countries are equally proficient. According to the **European CDC survey** conducted in **2018** and **2019**, only **60%** of laboratories were able to correctly identify a strain of ***C. auris*.**

C. AURIS Microbiologic Identification

On microscopy, ***C. auris*** is phenotypically indistinguishable from most other non albicans Candida spp.

The reliance on traditional methods that are based on biochemical assays may also lead to misidentification, due to a lack of reference databases . Examples of such biochemical assays are the VITEK® 2 (bioMérieux), BD Phoenix (Becton Dickinson),API® 20C AUX (bioMerieux), API® Candida and MicroScan (Beckman Coulter).

Indeed, several case series reported that the use of VITEK® 2 and API 20C initially misidentified ***C. auris*** in children .



Potential Misidentifications of *C auris*, Based on Identification Method

Identification Method	Organism *C auris* Can Be Misidentified As:
Vitek 2 YST	*Candida haemulonii* *Candida duobushaemulonii*
API 20C	*Rhodotorula glutinis* *Candida sake*
API ID 32C	*Candida intermedia* *Candida sake* *Saccharomyces kluyveri*
BD Phoenix yeast identification system	*Candida haemulonii* *Candida catenulata*
MicroScan	*Candida albicans* *Candida famata* *Candida guilliermondii* *Candida lusitaniae* *Candida parapsilosis* *Candida tropicalis*
RapID Yeast Plus	*Candida parapsilosis*

Recommended Diagnostic Methods for ***C. AURIS***

1. Correct *C. auris* identification requires specialized laboratory methodology, such as the use of matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDITOF MS), including reference *C. auris* spectra in the database.

2. Although less available for routine identification, molecular sequencing using polymerase chain reaction (PCR) assays offers definitive *C. auris* identification.

3. In contrast to biochemical automated systems and MALDI-TOF MS, which are culture dependent, DNA can be isolated directly from patients' specimens without the need for a culture. Therefore, molecular-based assays can provide rapid results, and carry the potential for high-throughput screening of surveillance samples in an outbreak setting.

C. AURIS Antifungal Resistance & Therapeutic Options

One of the main reasons for global concern about the spread of C. auris is its susceptibility profile, which limits treatment options.

Most isolates of C. auris are resistant to fluconazole, are often cross-resistant to other azoles, more than 90% of C. auris isolates have been reported to be resistant to fluconazole and have variably elevated minimum inhibitory concentration (MICs) for amphotericin B .

Echinocandins have the lowest MICs for C. auris of all systemic antifungal classes, but resistance to these drugs has been described.

The susceptibility categorization of C. auris isolates is based on tentative MIC breakpoints that were suggested by the CDC, based on those established for closely related Candida species and on expert opinion .

Table 2. Antifungals provisional breakpoint and resistance rate (RR) of *C. auris*.

	μg/mL [6], [14]	RR (%) [36]	RR (%) in Japan (see Table 3)
Fluconazole	32	44.3	15.4
Voriconazole	2	12.7	7.7
Micafungin	4	1.3	0
Caspofungin	2	3.5	0[a]
Amphotericin B	2	15.5	0
Flucytosine	128	2.0	0

HOW WOULD YOU TREAT THIS PATIENT?

Based on the above **MIC** data , concern for resistance to **azoles** and **amphotericin B** led the **CDC** and **Public Health England** to recommend **echinocandins** as first–line treatment of ***C..auris*** infections.

As a future treatment option, trials on **ibrexafungerp & rezafungin** are ongoing.

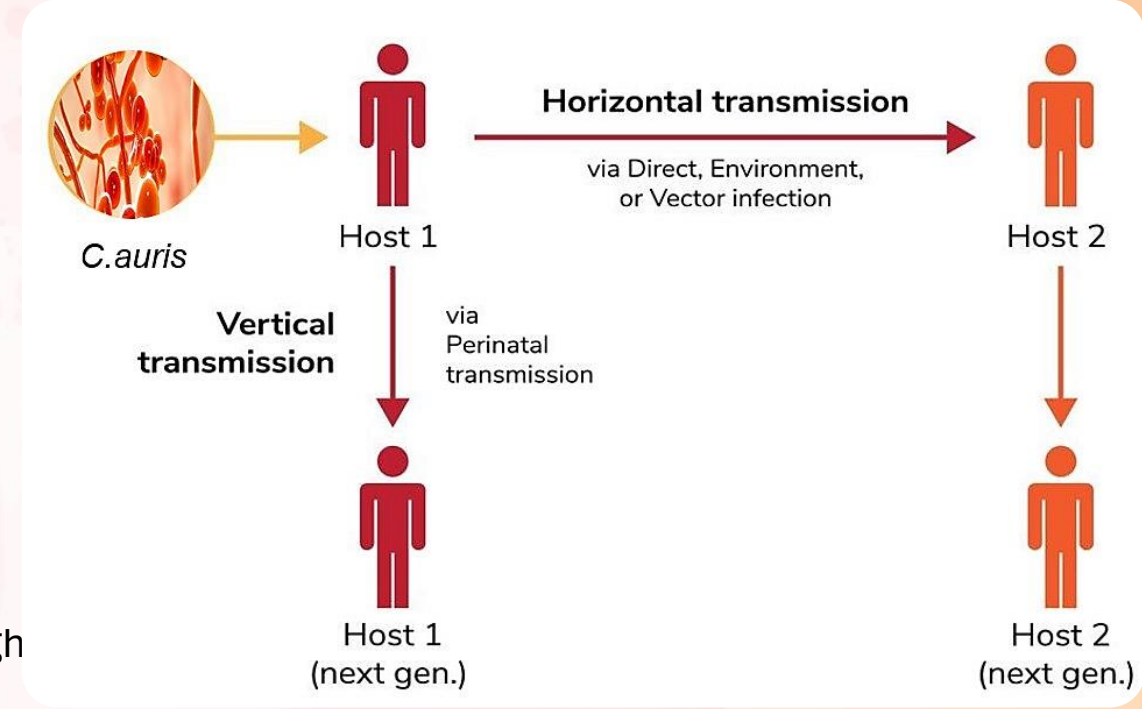
CDC Recommendations of First-Line and Alternative Treatment Options for Patients With *C auris* Infections

Patient Population	First-Line Therapy	Alternative Therapy (in patients who are unresponsive to first-line therapy or with persistent fungemia >5 days)
Adults (aged ≥18 years)	***Anidulafungin:*** Loading dose: 200 mg IV x1, maintenance dose: 100 mg IV daily ***Caspofungin:*** Loading dose: 70 mg IV x1, maintenance dose: 50 mg IV daily ***Micafungin:*** 100 mg IV daily	***Liposomal amphotericin B:*** 5 mg/kg/day IV
Children aged ≥2 months	***Caspofungin:*** Loading dose: 70 mg/m²/day IV, maintenance dose: 50 mg/m²/day IV (based on body surface area) ***Micafungin:*** 2 mg/kg/day IV; may increase to 4 mg/kg/day IV in children 40 kg	***Liposomal amphotericin B:*** 5 mg/kg/day IV
Neonates and infants aged <2 months	***Amphotericin B:*** deoxycholate 1 mg/kg/day IV	***Liposomal amphotericin B:*** 5 mg/kg/day IV ***Caspofungin:*** 25 mg/m²/day IV (based on body surface area)[a] ***Micafungin:*** 10 mg/kg/day IV[a]

[a] *Use with caution. Central nervous system involvement must be definitively ruled out. Source: Reference 15.*

Infection Control Measures against ***C. Auris***

- The remarkable widespread **horizontal transmission** of ***C. auris*** between patients in healthcare facilities is a **source of nosocomial outbreaks**.
- This is likely due to the capability of ***C. auris*** to **colonize the skin** of patients and healthcare personnel and to **survive** outside the host on **environmental surfaces** and **medical equipment** for long periods of time . Moreover, the pathogen is **resistant** to commonly used **disinfectants**, such as **quaternary ammonium compounds**.
- Outbreaks of ***C. auris*** have also been reported in designated **adult COVID-19 units** in India, Colombia, Mexico and the US. **Vertical transmission** was suspected, from a ***C. auris*** colonized mother through vaginal delivery to her offspring.



Infection Control Measures against *C. Auris*

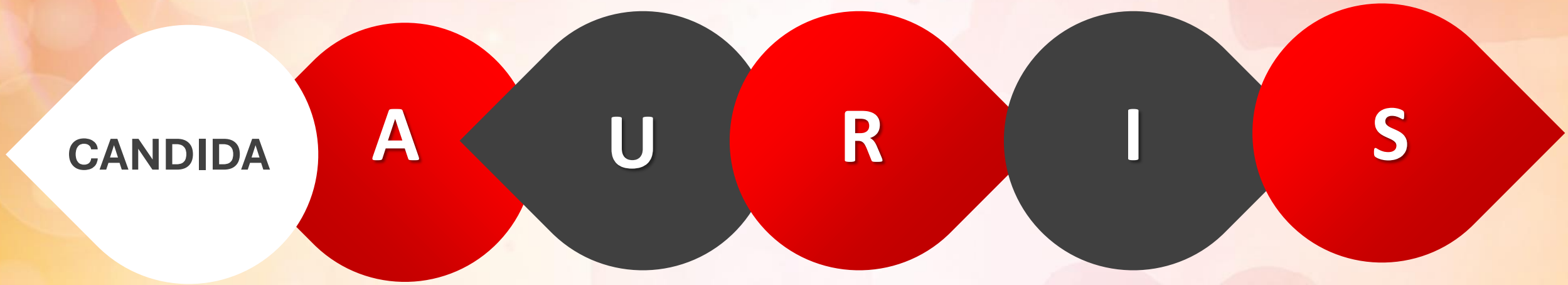
The primary infection control measures for prevention of *C. auris* transmission in healthcare settings are:

- Adherence to **hand hygiene.**
- Appropriate use of Transmission-Based Precautions based on setting.
- **Cleaning and disinfecting** the patient care environment (daily and terminal cleaning) with an Environmental Protection Agency (EPA)-registered hospital-grade disinfectant listed on EPA List K, a list of disinfectants that are effective against ***Clostridioides difficile*** .
- **Think beyond just high-touch surfaces** C. auris has also been identified on mobile equipment, such as glucometers, temperature probes, blood pressure cuffs, ultrasound machines, nursing carts, and crash carts.
- **Screening** contacts of newly identified case patients to identify C. auris colonization.
- **Laboratory surveillance** of clinical specimens to detect additional cases.

ALERT
Isolation in 5 continents

RESILIENCE
Persistent environmental contamination
Vicious cycle of acquisition, spreading & infection in ICU
Inactivity of common disinfectants

SURVEILLANCE
Need for antifungal resistance monitoring worldwide



ANTIFUNGAL RESISTANCE
Nearly 40% of MDR isolates
Pan-drug resistances reported

IMPLEMENTATION OF IPC MEASURES
Ability to perform outbreaks
Contacts tracing & screening of colonized & infected patients

THANK YOU