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Abstract

Candida auris was first described as a yeast pathogen in 2009. Since then, the new species has emerged worldwide. In contrast to most other *Candida* spp., *C. auris* frequently exhibits multi-drug resistance and is readily transmitted in hospital settings. While most isolations so far are from colonized patients, *C. auris* does cause life-threatening invasive infections. During management of the first documented *C. auris* transmission in a German hospital, experts from the National Reference Centers for Invasive Fungal Infections (NRZMyk) and the National Reference Center for Surveillance of Nosocomial Infections screened available literature and integrated available knowledge on infection prevention and *C. auris* epidemiology and biology to enable optimal containment. Relevant recommendations developed during this process are summarized in this guidance document, intended to assist in management of *C. auris* transmission and potential outbreak situations. Rapid and effective measures to contain *C. auris* spread require a multidisciplinary approach that includes clinical specialists of the affected unit, nursing staff, hospital hygiene, diagnostic microbiology, cleaning staff, hospital management and experts in diagnostic mycology / fungal infections. Action should be initiated in a step-wise process and relevant interventions differ between management of singular *C. auris* colonized / infected patients and detection of potential *C. auris* transmission or nosocomial outbreaks. [*word count* 205]

Keywords: *Candida auris*, Expert recommendation, Infection Prevention, Nosocomial transmission

Introduction

Candida auris was first described as a causative agent of otomycosis in Japan in 2009 [1]. Since then, the species has spread globally. *C. auris* has been isolated from various clinical materials, both as a causative agent of invasive infections and as a colonizer [2-5]. Initially, identification of *C. auris* in the clinical laboratory was highly problematic because the new species was not included in evaluation databases for diagnostic procedures such as biochemical tests and mass spectrometry (MALDI-TOF) [6]. In the meantime, identification by MALDI-TOF is straightforward if up-to-date technologies and databases are used [7]. Consequently, a German national ring trial showed that 85% of 233 participating laboratories succeeded in correctly identifying *C. auris* already in 2018, (personal communication G. Haase, Aachen, Germany). However, other European quality control trials show less reassuring results recently [8, 9]. As an alternative to MALDI-TOF, identification of *C. auris* can be reliably confirmed by sequencing of the internal transcribed spacer region (ITS1, ITS2).

C. auris - similarily to closely related species in the *C. haemulonii* group - frequently shows high minimum inhibitory concentrations (MICs) for various antifungal agents. More than 80% of known isolates have high MICs for fluconazole [10, 11]. Consequently, fluconazole is not a therapeutic option for almost all clinical cases of *C. auris* infection. About 50% of isolates additionally show high MICs for voriconazole and other new-generation azole antifungals, which likely argue for ineffectiveness of these agents. However, clinical cut-off values have not been described and clinical proof for relevant MIC-outcome relation is absent for the species [12, 13]. In addition, about one third of *C. auris* isolates show amphotericin B MICs of > 2 µg/ml [13, 14]. It remains unclear whether this can predict therapeutic failure. Finally, *C. auris* has been shown to potentially exhibit echinocandin resistance, which in most cases is due to target mutations in the FKS gene [15-17]. Pan-resistant *C. auris* strains have been described [18].

Apart from its intrinsic ability to exhibit and / or develop antifungal drug resistance, *C. auris* is readily transmitted in hospital or nursing home settings. Case clusters of *C. auris* infections and detections with unclear clinical relevance/colonization have been described in numerous locations [19-25]. In 2015 / 2016, 50 *C. auris* detections occurred in a cardiac surgery unit at the Royal Brompton Hospital, London within 16 months. Fifty-six percent of cases (28 of 50) were pure colonization, and 16% of cases (9 of 50) were bloodstream infections [19]. In an intensive care unit at Oxford University Hospital, *C. auris* detections occurred in a total of 70 patients between 2 / 2015 and 8 / 2017, including 7 clinically relevant cases and could be linked to the use of

reusable skin-surface axillary temperature probes [20]. Further European outbreaks, some with > 100 affected patients have been described in the United Kingdom and in Spain [2, 3].

Transmission of *C. auris* occurs mainly directly or indirectly via smear infection. Surfaces close to patients and devices / medical devices that come into direct contact with patients regularly play a central role in case clusters [19, 20, 26]

In Germany, only isolated cases of *C. auris* had occurred until the end of 2020 [7]. These recommendations result from management of the first documented *C. auris* transmission event in Germany and was developed as a joint effort of the German National Reference Centers for Invasive Fungal Infections and Surveillance of Nosocomial Infections. They are mainly based on expert opinions and are suitable for countries with a highly developed health system and a low prevalence of *C. auris* only.

Our recommendations are structured into three sections (Figure 1). Section A covers general recommendations for detection / identification of *C. auris* in the microbiological laboratory. Section B summarizes recommendations for clinical management of index-cases, i.e. first detections of patients colonized or infected with *C. auris* in an organizational unit. While recommendations in sections A and B are also applicable for situations where potential transmission of *C. auris* has occurred, usually no further measures are required for singular cases. In particular, comprehensive environmental and personnel investigations are not recommended. Recommendations in section C apply if there is evidence of transmission of *C. auris* to a second patient. Evidence of transmission is defined as the detection of *C. auris* in a second patient of the same organizational unit within 6 months of the index case. It is recommended that measures according to section C are initiated immediately if - after clinical evaluation - transmission is not judged highly unlikely for obvious reasons. In case of *C. auris* transmission, mandatory reporting of nosocomial outbreaks must be considered (§6 IfSG).

Recommendations

A; How should the microbiology lab diagnose *C. auris?*

A.1 Identify *C. auris* by MALDI-TOF.

Mass spectrometric identification of *C. auris* is reliably achieved with the systems commonly used in Germany, provided that up-to-date databases are used. While molecular identification via sequence analysis of the ITS1/2 region also allows reliable identification, it is time-consuming and unsuitable for routine diagnostics. Biochemical assays should not be used for identification as they may lead to delayed identification and misdiagnosis [7, 27].

A.2 Perform susceptibility testing for all *C. auris* isolates and confirm suspected echinocandin resistance by FKS sequencing.

Echinocandins, new generation azoles or amphotericin B may be suited for treatment of *C. auris* infection. However, *C. auris* shows highly variable susceptibility patterns and frequently exhibits resistance at the time of diagnosis or develops resistance during therapy [28, 29]. Thus, adjustment of therapy may be necessary and frequent susceptibility testing of follow-up isolates is required. However, test results are difficult to interpret and no EUCAST breakpoints for the species *C. auris* exist. Phenotypic resistance testing for echinocandins in *C. auris* is unreliable and often difficult to interpret. Thus, echinocandin resistance should be confirmed by FKS sequencing as recommended for other species that readily acquire resistance [30, 31]. Discontinuation of echinocandin therapy should not solely be based on phenotypic testing. If antifungal susceptibility testing is not available in the diagnostic laboratory, the NRZMyk offers free-of-charge testing.

A.3 Identify all yeast isolates from patients with a high risk for *C. auris* to the species level.

Currently (12/2021), less than 30 cases of *C. auris* have been identified in Germany since 2015 [7]. As occurrence of *C. auris* is currently rare, a generalized admission screening is not recommended. Based on current experience, most *C. auris* index patients in Germany are patients transferred from medical facilities in the Middle East (e.g. Arabian Peninsula), South-East Asia (e.g. India), South America and Africa, or from hospitals or facilities where *C. auris* cases are known [28, 31-34]. While in some cases, occurrence of *C. auris* in Germany could not be linked to

medical care abroad [7, 35], identification of *Candida* sp. from any clinical sample in such high-risk patients should be performed to the species level using MALDI-TOF, especially for non-*albicans* species (e.g., non-green colonies on Chromagar™ *Candida*).

A.4 Submit all *C. auris* isolates to the NRZMyk for typing, testing and storage.

There is no systematic surveillance of *C. auris* in Germany and no mandatory reporting of isolated cases. For continuous analysis of the epidemiological situation, *C. auris* isolates including all follow-up isolates should be sent to the NRZMyk. This enables precise typing and classification at clade level as well as tracing of possible transmissions. The NRZMyk publishes current figures for Germany, informs the Robert Koch Institute and participates in European data collections and worldwide research projects, thus making German data available to the public [2, 3, 7].

B; How should an (index-)patient colonized or infected with *C. auris* be managed?

B.1 Isolate patients infected and / or colonized with *C. auris* in a single room.

C. auris can spread as part of smear infections and can lead to prolonged, difficult-to-control outbreaks with significant impact on patient care and potentially life-threatening infections. Aerogenic spread can be ruled out with near certainty, and infections of the lungs have not been described to any relevant extent, analogous to other *Candida* spp. Consistent with relevant CDC and ECDC recommendations (https://www.cdc.gov/fungal/candida-auris/health-professionals.html; https://www.ecdc.europa.eu/en/publications-data/rapid-risk-assessment-candida-auris-healthcare-settings-europe), isolation of patients infected or colonized with *C. auris* in single rooms is essential. Education of staff and visitors on the relevance of hand disinfection with alcohol-based disinfectants should be provided. Medical devices should be specifically assigned to the patient and not be used for other patients.

B.2 Ensure the usage of personal protection equipment and hand hygiene during patient attendance. A 1:1 care of the patient is advisable.

For nursing, 1:1 care of the patient should be ensured. Medical personnel should wear a long-sleeved disposable gown and disposable, germ-free gloves when providing nursing and medical care to patients. Hand disinfection in accordance with the WHO approach of the “5 Moments for Hand Hygiene” is strongly recommended (https://www.who.int/campaigns/world-hand-hygiene-day). Commercially available alcohol-based hand sanitizer are suitable for hand disinfection in *C. auris* patients. The “Aktion Saubere Hände” (https://www.aktion-sauberehaende.de/) provides further information on correct hand hygiene.

B.3 Inform / teach medical and nursing staff in the affected organizational unit about *C. auris* and the associated risks.

In contrast to other nosocomial problem germs, *C. auris* is usually little or not at all familiar to medical and nursing staff. Medical and nursing staff should therefore be informed about *C. auris*, in particular about the risk of multi-resistance, transmission through smear infections (direct and indirect), the importance of hand hygiene, surface cleaning / disinfection and the optimal handling of medical devices close to the patient. Not only health care personnel of the affected ward (organizational unit), but also staff from affiliated areas of patient care should be informed. These

may include (among others): radiology facilities, consulting physicians, general practitioners, physiotherapists, or facilities / wards where *C. auris* patients are transferred to. The NRZMyk can support with materials with regard to these information events.

B.4 Amend disinfectant procedures concerning patients infected and / or colonized with *C. auris*.

With regard to the cleaning and disinfection of patient rooms and medical equipment, the disinfectants should be changed if necessary. To ensure safe inactivation of *C. auris,* peracetic acid (PPA) based disinfectant should be used instead of those consisting of quaternary ammonium compounds (QAC) with or without alcohol. It is recommended to change the disinfection of the ultrasound probes from disinfectant wipes with QAC to wipes with hydrogen peroxide as these sensitive probes must not be cleaned with an alcohol. Disinfection of other medical devices or surfaces in the hospital should continue with alcohol-based disinfectants.

B.5 Initiate antifungal therapy only if *C. auris* is related to clinically relevant infection.

In many cases, *C. auris* occurs as a colonizer without disease significance (e.g., detection in tracheal secretions, detection from indwelling catheter urine, detection on the skin). In these cases, antifungal therapy is neither necessary nor useful. There are insufficient data on decolonization [36-39]. In the context of skin colonization, the *in vitro* efficacy of preparations containing chlorhexidine, has been demonstrated in some studies. In other cases, however, pathogen persistence was reported despite multiple antiseptic washes with chlorhexidine [37]. Nitroxoline exhibits anti- *C. auris* activity *in vitro* and might be of use in urinary tract decontamination although clinical data are lacking [40].

If antifungal therapy is required, fluconazole should not be used. A decision to use other new-generation azoles should be made on a case-by-case basis. Echinocandins are a suitable option for primary therapy, although resistance may occur (see section A, [17, 29]). Liposomal amphotericin B is a suitable option for primary therapy although some data indicate variable *in vitro* fungicidal activity [41]. Strains with elevated MICs have been described in the literature; currently, it is unclear to what extent these elevated MICs always or in individual cases correlate with treatment failure [42]. Infectious diseases consultation is highly recommended. For life-threatening *C. auris* infection, combination therapy may be warranted at least initially to ensure antifungal activity prior to availability of reliable antifungal susceptibility testing results.

B.6 Screen close contacts of the index case for *C. auris* colonization.

Patients with relevant contact to an index case (e.g. stay for > 24h in the same room, use of same medical devices across patients) should be tested for colonization with *C. auris*. At least the following materials are recommended for screening: (i) axilla swab bilaterally (one swab [standard swab for bacteriological testing, with standard transport medium if necessary]), (ii) inguinal swab on both sides (one swab), (iii) naso- / oropharyngeal swab, (iv) urine (catheterized patients only), (v) rectal swab [43]. According to recently published data the latter shows more reliable positivity rates over time (in comparison to skin swabs only) and provides a correlation to *C. auris* UTI [55]. Screening samples should be examined by culture using a chromogenic selective medium, which enables identification of *C. auris* (see C.4, Figure 2) or alternatively enables species identification of all non-*albicans* isolates by MALDI-TOF. De-isolation of close contact patients should only be done after final negative screening results are available.

C. How should potential nosocomial transmission of *C. auris* be managed?

C.1. Set up a multi-disciplinary outbreak panel.

Management of potential *C. auris* transmission is challenging and requires a multi-disciplinary approach. It is therefore recommended to set up an outbreak panel including at least the following institutions / areas / expertise: (i) representative(s) of the affected organizational unit, (ii) hospital hygiene, (iii) diagnostic microbiology laboratory, (iv) facility / cleaning service, (v) management of the affected institution. The NRZMyk offers advice / participation in such panels. The panel should jointly organize action as recommended in C.2-9 and in addition set up internal and external communication, the latter initially and obligatory with public health authorities. Communication with the press may also become necessary.

C.2 Set up a work-flow for *C. auris* screening with the diagnostic lab which should use color indicator media able to detect *C. auris* as they considerably facilitate pathogen detection.

A clearly defined work-flow for submission of screening samples to the diagnostic lab should be set up. Standard color indicator media do not reliably identify *C. auris*. For example, different shades of color have been described on Chromagar™ *Candida*, and colonies often remain largely colorless for a longer period of time [7]. Therefore, special color indicator media such as Chromagar™ *Candida Plus* should be used for screening and cultural detection in outbreak situations [44, 45] (Figure 2). *C. auris* suspect colonies appear light blue on this color indicator medium with a blue rim on the front side as well as with a blue background on the back side. MALDI-TOF based verification can be performed directly from the plate.

C.3 Stop admissions of patients to the affected organizational unit

No patients should be transferred to the affected organizational unit until the extent of nosocomial transmission is determined and potential transmission routes have been identified. Moreover, *C. auris* colonized or infected patients must be isolated in a separate area of the ward (see C.4). Alternatively, the admission stop should continue until all *C. auris* patients are discharged.

C.4 Create separate areas for *C. auris* colonized / infected patients and unaffected patients within the affected organizational unit.

In general, individual housing of patients infected with *C. auris* is appropriate. Separation of an area for infected patients at a distance from non-infected patients should be aimed for. Patient-related equipment (ultrasound, tracheostomy sets, etc.) should be used separately for infected / colonized versus unaffected patients.

Whenever possible, there should be a switch to single-use / disposable devices. Disposable protection should be used for near-patient equipment (e.g. ultrasound). Where the use of jointly used medical devices and equipment (e.g. X-ray examinations, ECG equipment, physiotherapeutic equipment, etc.) is unavoidable, these must be thoroughly disinfected with *C. auris* active disinfectants before and after use in accordance with the manufacturer's instructions and observing the correct exposure time.

Terminal cleaning and disinfection of patients' rooms and any other areas in contact with patients need to be disinfected using appropriate disinfectants. Disinfectants based on QAC should be strictly avoided (see C.7).

C.5 Test all patients in the affected organizational unit for *C. auris.*

Screening of all patients in the same organizational unit where a potential transmission has occurred should be performed immediately, with sampling analogous to recommendation B.3. In addition, swabs from other typical colonization sites such as wounds, external auditory canal, rectum or vagina may be considered depending on the clinical situation. Two initial screenings (day 0; day 4) within the first week, accompanied by a once-weekly-follow-up were found to be helpful.

Patients who were cared for in a relevant period of time in the organizational unit affected and who were discharged or transferred in the meantime should also be examined. At least patients with regular contact to the health care system require testing. To date, no data exist to define the relevant time period for screening or tracking patients. Ideally, screening should start with admission of the index case to the organizational unit. If this is not possible, it is recommended that the time period should be at least 7 days before detection of the second case.

C.6 Review and amend hygiene plans in the organizational unit with regard to the use of potentially poorly effective disinfectants.

For surface disinfection, products based on QAC should be avoided, as available data suggest insufficient efficacy on *C. auris* (and also other *Candida* species). In contrast, disinfectants that contain relevant alcohol components in addition to QAC can be expected to be effective [46-50]. In case of doubt, a switch to alcohol-based disinfectants should be made. Daily disinfecting cleaning of the patient's room is routinely implemented at intensive care units and is recommended for normal wards caring for a *C. auris* colonized / infected patient. Disinfectants on the basis of PPA or alcohol (for smaller surfaces) are recommended. Particular attention should be paid to frequently used surfaces (patient tables, bedside cabinets, bed rails, etc.). The adherence to these measures should be monitored closely by certified and experienced cleaning personnel (e.g. trained disinfector).

C.7 Analyse potential transmission routes.

As immediate action, detailed analysis of work processes and patient file analysis are advisable in identification of potential transmission routes. Based on these findings, environmental and patients' screenings can be useful to confirm suspected transmission routes. If unsuccessful, case-control / cohort studies may be considered at a later stage. In order to ensure a targeted follow-up of possible transmission routes, primarily medical devices, medical equipment and examination methods that are directly connected with affected patients and have been used on them should be checked for possible transmission of *C. auris*. These may include (i) medical devices used on patients on a daily basis (e.g. blood pressure cuff, sandbags, other aids); (ii) medical devices in direct patient contact including bronchoscopy, laryngoscopy, orthoscopy, cystoscopy) (https://www.cdc.gov/fungal/candida-auris/health-professionals.html;); (iii) medical intervention such as tracheostomy and other surgical procedures, emergency events.

Broad environmental screening or PCR studies to analyze possible routes of transmission have so far not proven useful [19, 20]. Thus, environmental screening should only be considered for targeted issues. Staff testing has not made a relevant contribution to outbreak control or detection in past outbreak events. For example, during outbreak control at the Royal Brompton Hospital, London, 5 swabs each (hands, nose, axilla, groin, throat) were taken from 258 individuals as part of a staff screening program. A total of one transient carrier was identified (positive nasal swab, other materials negative), but the affected person had contact with only one patient and was not a

source of dissemination according to epidemiological analyses [19]. Therefore, broad healthcare worker investigations are not recommended.

C.8. Implement strict rules for de-isolation of formerly infected / colonized patients.

Colonization with *C. auris* can persist for a long period of time, with CDC describing colonizations for longer than 1 year (https://www.cdc.gov/fungal/candida-auris/health-professionals.html;). A possible cease of isolation measures should thus be done restrictively and not considered within 3 months after a positive culture. Release from isolation during antifungal or local antiseptic therapy is not appropriate – antifungal therapy should have been stopped at least 7 days before testing. At least two swab series (bilateral axilla, bilateral inguinal + any site of last colonization) taken at least one week apart should be culturally negative. In addition, we recommend that *C. auris* PCR testing should be used for analysing the second swab set to enhance sensitivity. Several feasible PCR protocols have been described and tested [51-54]. Screenings prior to readmission to hospitals / health care facilities - analogous to other common multi-drug resistant organisms - are be advisable.

C.9 Perform long-term surveillance for the presence of *C. auris* in organizational units with documented transmission.

Outbreaks with *C. auris* are prolonged and new cases may occur over the course of several weeks or months. We recommend that even in the absence of further cases, patients in the affected organizational unit should be screened for *C. auris* at least once a week with a combined groin-axilla smear (culture only) for at least 3 months after the last positive patient has been discharged. In addition, weekly screening of urine samples for *C. auris* is recommended for patients with urinary catheters, as urinary tract catheters have frequently been colonized with *C. auris* in cases observed in Germany so far. Furthermore, rectal swabs may enhance screening sensitivity. The use of specific color indicator culture media is useful for this purpose (Figure 2). For the same period of time (at least three months), a systematic differentiation of all yeasts detected from clinical materials of the affected ward / organizational unit down to species level is recommended.

Conclusion

The emergence of *C. auris* poses a new risk for healthcare worldwide. While multiple outbreak descriptions exist and systematic analyses of this novel pathogen have started to shed some light on the specificities of its emergence and optimal control measures, solid evidence regarding most if not all clinically relevant interventions is still missing. Based on real-life management of a transmission case, these recommendations were compiled to aid clinical management of *C. auris* transmissions in future cases.

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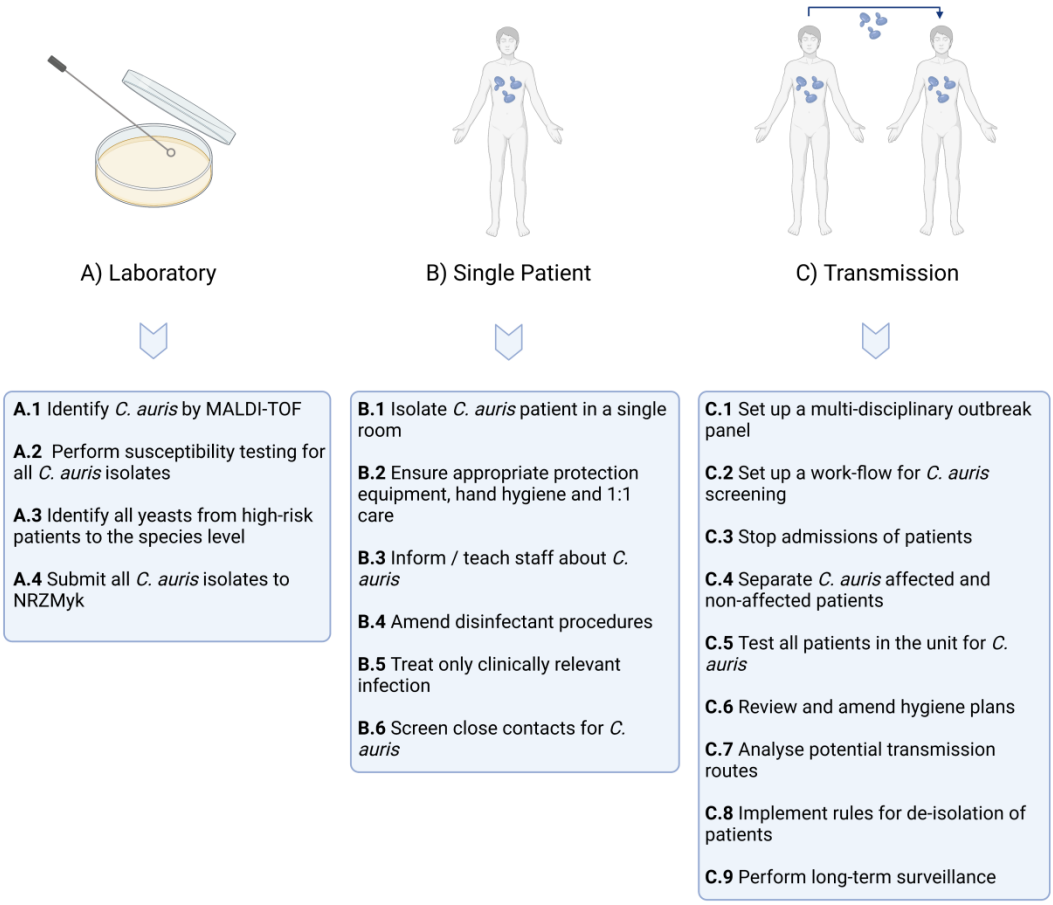
Figure Legends

Figure 1 – Summary of recommendations (A) for laboratory procedures, (B) in case of identification of a single patient colonized or infected with *C. auris* and (C) in case of potential transmission events.

Figure 2 – Appearance of *C. auris* (A) on standard fungal medium (Sabouraud-Dextrose Agar), Chromagar *Candida*™ with unspecific colouring and Chromagar *Candida plus*™ with a specific light blue color, a blue rim on the front side and a blue-green background on the back side (all: 48 h incubation at 35°C) and (B) in brightfield (left) and fluorescence (richt, stained with Calcofluor White) microscopy .



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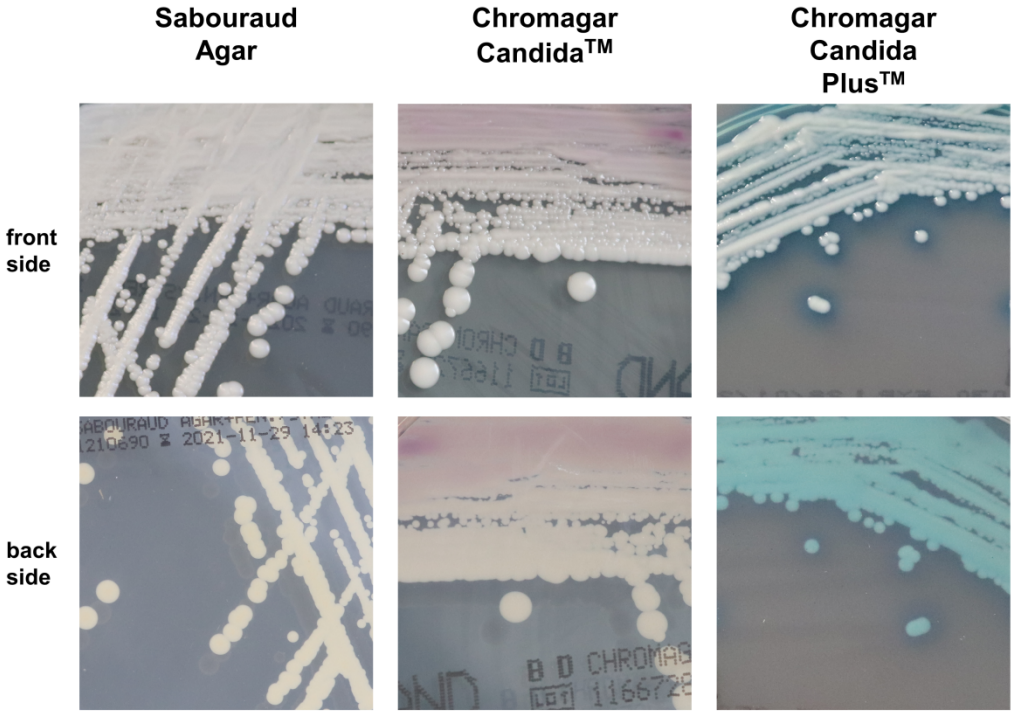

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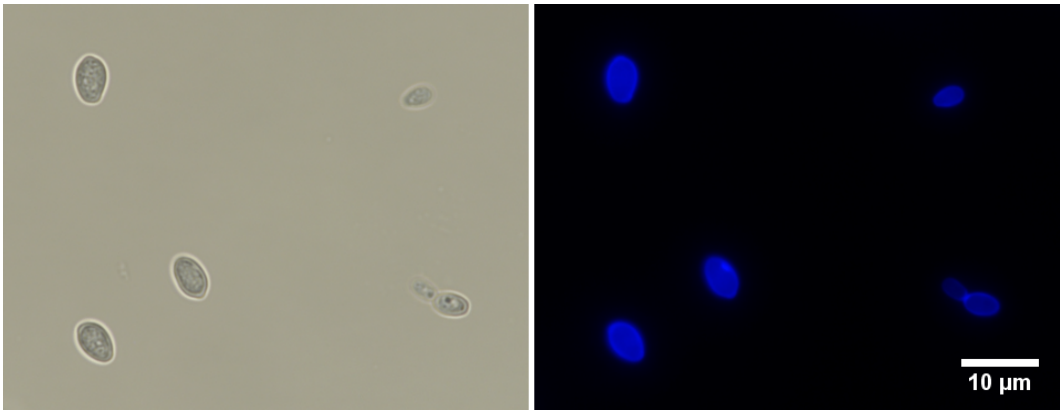

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